## article Title

**Challenges in designing clinical trials to test new drugs in the pregnant woman and fetus**

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## Keywords

4-8 keywords to enhance online search results

Pregnancy, drug development, clinical pharmacology, ethics, public private partnership

## Key Points

3 to 5 bullet points of approximately 25 words each that summarize the main ideas of your article. Key points appear at the very beginning of your article in print and online.

* The development of new drugs to treat maternal and fetal conditions can be improved using approaches that are succeeding in other marginalized therapeutic areas.
* Improved information about the risks and benefits of interventions during pregnancy is needed to facilitate study design and review by ethics boards, regulators, funders and potential participants of studies
* It is important to ensure that the design and conduct of in vitro, ex vivo and clinical studies are compatible with the needs of drug development programs
* Collaboration in effective geographical and methodological, pan-stakeholder public-private partnerships, with global coordination, is essential to overcome the problems that arise during research about new drugs in pregnancy

## Synopsis

Brief summary of your article (100 words or fewer; no references or figures/tables). The synopsis appears only in the table of contents, and is often used by indexing services such as PubMed.

The need for new drugs in pregnancy is widely recognised. This review identifies a number of specific challenges and describes some solutions. Specific studies and drug development programmes need careful planning that accounts for the needs of regulatory agencies. The perinatal (obstetric / paediatric) community needs to join collaborations to develop methodologies, to facilitate data sharing, and to lobby for research and access to medicines. There is a need to gather and present information that promotes proportionate judgments of the balance between potential benefits and risks. This will require researchers to look beyond their traditional ways of working.

**INTRODUCTION**

The paucity of information about drugs used in pregnancy and the need for new drugs have been described elsewhere1-7. The marked lack of information to support prescribing drugs for pregnant women who present with intercurrent illness, specific conditions of pregnancy or fetal conditions reflects a number of problems: science, trial recruitment, ethics, legal factors etc. This review examines some specific challenges that arise from taking a comprehensive approach to these interconnected problems (see Table 1). We outline actions that can be taken by individual drug development programmes and actions that are required from the whole materno-fetal community.

**CHALLENGES**

Profound changes in maternal physiology fundamentally alter pharmacokinetics and pharmacodynamics, often in an unpredictable fashion. There are three discrete and intimately dependent units comprising of the mother, the fetus and placenta. The placenta, once thought to be a passive filter between the maternal and fetal compartments, is in fact a highly complex organ rich in transporters. The human placenta remains relatively understudied, particularly in early healthy pregnancy. Comparative placentology has yet to identify an ideal animal model8. Whilst humans share a haemochorial placental structure with the great apes and some rodents, there are some important differences which preclude robust extrapolation. For this reason, there has been much interest in evaluating transplacental transport using the ex vivo placental cotyledon model (for a review see9)

A significant challenge is that the current regulatory environment somewhat ironically does not require drug research in pregnancy whilst at the same time allowing off-label use in this population.

*Models*

If experimental models are to make a meaningful contribution to drug development 10-12 then research needs to follow best practice. Research should be reproducible within and between laboratories (https://www.nature.com/collections/wjsrmrdnsm#features). This includes paying attention to validation (is the data precise and reproducible) and qualification (does the data do something useful in a specific context of use)13.

There are some examples of work towards validation of placental models. Myllynen et al. assessed four model compounds using the dual-perfused placental cotyledon model in two laboratories14. Conings et al. identified several quality control measures for the same model in a single laboratory15. However, this work needs to be extended so that these and other models are sufficiently rigorous to inform drug development. Standardised approaches are being developed by an international human placental testing platform (PlaNet)16. The importance of careful attention to validation during academic research is demonstrated by Prinz who examined 67 attempts to reproduce literature findings in a single large Pharma company17. In 43 cases (65%) the in-house findings of an experienced and well-resourced lab were not consistent with the literature so that majority of therapeutic suggestions from the literature were “false positives”17.

*Regulatory issues*

The FDA issued an updated draft guidance about drug development during pregnancy in 201818. Ethical criteria over a range of stages in clinical drug development covering maternal and fetal indications have been suggested19. Academics who want to promote drug development need to gather more information than is needed for a publication. Many academics aim to influence their peers through grant applications and publications. It is also important to influence decision-makers such as industry, regulators, health services and the agencies that reimburse costs. This requires an awareness of the information needed by each decision-maker, and linking in vitro studies to clinical studies. Careful planning avoids wasted effort20 and will de-risk drug development21.

Studies that will be submitted to regulatory agencies need to meet relevant guidelines such as the “Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals M3 (R2)”

<http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M3_R2/Step4/M3_R2__Guideline.pdf>

Data sharing can facilitate drug development. Data should be collected in such a way that it can be added to generalizable pools such as physiologically based pharmacokinetic models through standardised definitions and data standards22. Making the most of existing data allows extrapolation or modelling to help design trials18. While extrapolation from animal models of pregnancy is challenging, well-defined physiological models using published human data can underpin pharmacokinetic studies 22, 23.

There is a perception, with respect to study of drugs in pregnancy, that “a single FDA regulator may be in a position to derail a study, even one that has been approved by the IRB and survived scrutiny from internal or external legal counsel, because of different interpretations about legally (or perhaps institutionally) acceptable levels of risk”24. This may relate to the different perspectives of risk that institutions have due to legal constraints or from experience. Alternatively, it may reflect unnecessarily conservative attitudes to risk within an institution. In either case, it is important to pool experience and promote understanding of multiple perspectives so that shared expectations can be developed. Public private partnerships can contribute to shared understanding, preferably when they address issues that are relevant to all projects, that is precompetitive.

*Legal*

Pertinent legal issues include different interpretations of the law, non-legal constraints on decision-making such as finance or reputational issues, and ambiguities in the legal and regulatory texts24. Ambiguities related to the definition of “minimal harm” and “prospect of direct benefit” are particularly troublesome. In legal argument, the lack of evidence about likelihood of fetal harm or benefit leads to uncertainty which promotes a conservative interpretation of the law and regulations. This is further compounded by the differing legal status of the fetus versus the mother internationally. In some jurisdictions the fetus has a greater degree of legal protection than in others which makes the risk benefit ratio judgement complex and ambiguous across multiple jurisdictions. The risk of liability is important, but is not specific to maternity research. The specific problems for liability in pregnancy arise from: a) the “long-tail problem”, e.g. diethylstilboestrol (DES); b) the magnitudes of potential effects, e.g. thalidomide. This discourages pharmaceutical companies from accepting the risks arising from use of their products in pregnant women. Compensation from harm arising during clinical trials varies between countries and this can increase reluctance for US companies (that do not need to provide this compensation) to conduct research in other countries24.

While some of these problems cannot be resolved directly, action by the materno-fetal community on some points will be beneficial:

1. Taking account of influences on legal perspectives (law, widely accepted guidelines) in addition to family, clinical, regulatory and commercial perspectives.
2. Shared understanding of terms such as minimal harm and direct benefit, as they apply in pregnancy – including different stages of pregnancy
3. More information about harms and benefits that can inform judgments
4. Precedents for successful management of risk and liability (including insuring clinical trials) with a focus on the rationale for these successes and legal arguments used
5. Many adverse fetal outcomes are rare (death disability etc.) and therefore observational cohort studies and clinical trials need to be very large

*Registries*

Clinical trials provide limited information during the development of new drugs. Accordingly, it is important to setup registries for women and their offspring who are exposed to new drugs. The concept of registries of drug exposure during pregnancy have been described, including ethical aspects25. Observational studies of drug safety have been conducted during pregnancy26, but high quality studies of adequate size are rare. The assessment of potential adverse drug reactions can be challenging. Tools such as the Naranjo score do not take account of pregnancy so that population-specific tools need to be developed and validated. As an example, pediatric-specific tools have been developed27-29.

Registries can also provide information to support the design of clinical trials. Considerable methodological challenges need to be addressed. One challenge relates to data quality and the ability to share data across similar studies and reuse data for a different purpose than initially intended. Core outcome sets have been promoted as one way to meet this challenge but do not address the challenge completely30. Data standards are a useful approach that standardise data collection and allow legitimate variation in the selection of outcomes (Costeloe, in press). Registries should not be drug-based but need to be participant-based or even population-based. Registries are expensive and costs need to be shared between the stakeholders who will benefit from them.

*Maternity Investigation Plan*

This suggestion1 relates to a pregnancy analogue to the Paediatric Investigation Plan (PIP) in Europe31 and to the Pediatric Study Plan in the US32. There are two aspects to a PIP: content and importance. The **content** of a Maternity Investigation Plan is relatively easy to state, based on FDA guidelines [FDA 2018] taking account of the different uses of drugs in pregnancy such as maternal concurrent illness, maternal pregnancy-related complications and fetal indications19. The **importance** of the PIP stems from its status as a legal requirement for all drug development programmes that are relevant to paediatrics.

Senior members of the EMA have written: “Regulators should require comprehensive information regarding safety and efficacy of medicines in pregnancy and apply a much more systematically balanced and all-encompassing approach regarding the inclusion and follow-up of pregnant women in well-designed clinical trials and postauthorization, rather than excluding them systematically from clinical trials”33. However, regulators can only implement the law and a change in practice by regulators requires a change in law. Examples of the changes in legal mandate required to change regulatory practice are the long process that led to the current requirements for pediatric studies in the US and the PIP in Europe. In the US, impetus for legislative efforts related to pregnancy may come from a task force established by The 21st Century Cures Act, the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC). PRGLAC reported to the Secretary of Health and Human Services in September 2018 about gaps in knowledge and research on safe and effective therapies for pregnant women and lactating women and made specifc suggestions for changes in US legislation and policy (https://www.nichd.nih.gov/About/Advisory/PRGLAC, see below) . Challenges of development plans include discordant approaches across jurisdictions. In other therapeutic areas, these can be addressed in discussions between regulators34.

*Involvement and Engagement*

Identification of research needs, and the design and conduct of trials need to involve potential participants and their families35-39. Specifically, women indicate that their informed choices must be based on information about the risks related to the study. A sensitive approach must take into account their needs and perspectives in the specific context that the trial addresses. Since pregnancy encompasses a vast range of physiological, emotional and pathological states each trial team needs to undertake preparatory work about the information needs, and communication preferences, of potential participants.

**FUNDING**

Globally, the allocation of resources to the development of new drugs is controversial40 and pharmaceutical companies currently have many reasons to avoid investing in pregnancy research24. As noted in the legal section of this review, downside risks are highly visible (legal liability etc.) and compare unfavourably to any potential financial benefits. Information about the burden of disease is available but needs to be presented more effectively to decision-makers in companies, government and public funders. Widespread off-label or off-evidence use also undermines incentives to drug development. Fisk outlined the issues relating to commercial drug development in 20083. The situation has not changed in the past decade, except that even fewer drugs are under commercial development. The health economic considerations related to the development of new drugs for pregnant women have been described41.

Broader pharmaceutical policy may offer some solutions relating to early-phase push (such as public funding for research that does not depend on subsequent profits) and late phase pull mechanisms (such as legal and regulatory facilitation, reimbursement advantages, prizes or predictable reimbursement through insurance-like models). The example of antibiotics illustrates the strengths and weaknesses of these approaches and the need for global coordination and oversight42. The costs and benefits of each approach need to be considered carefully43. Efficient research requires incentives for academics and “hidden” contributors to drug development such as the sites that host research. Relevant actions are summarised in Table 2. Individual researchers and Sponsors will not be able to gather all the information that is required to change the funding environment: another potential task for public-private partnerships.

**ETHICS**

The ethics of research involving pregnant women may seem straightforward. For example, a 1994 report by the US Institute of Medicine recommended that “pregnant women be presumed to be eligible for participation in clinical studies”44. International ethical guidance also promotes appropriate research that recruits pregnant women (CIOMS 2016; <https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf>). On the other hand, a systematic review of ethical issues that arise during research about vaccines that recruits pregnant women found 60 separate issues45. Experience indicates that the clear, international consensus statements are often not reflected in daily research practice and attitudes to research46.

Some of the complexity arises from different frameworks for reviewing research. Emanuel identifies four paradigms for research review: researcher paternalism; regulatory protectionism; participant access; community participation47. Among ethical and legal reviewers “regulatory protectionism” appears to be the dominant paradigm48. Many clinicians work with the “participant access” paradigm. “Community participation” is less well developed among the materno-fetal community than among other populations, such as HIV. Within drug development programmes it is important to recognize the paradigm that reviewers are using so that data and justifications can be presented appropriately. The choice of paradigm is not easy to change and will require influence across the materno-fetal community. No matter which paradigm is used, the core task is to gather sufficient data to allow skilled judgments about trade-offs in trial design (see below for comments on making skilled judgments). This will require information that researchers do not usually gather when developing new drugs.

Pregnant women are seen as vulnerable. A review of the concept of vulnerability with respect to pregnant women in research argued that vulnerability can manifest in four ways: (i) informed consent, (ii) susceptibility to coercion, (iii) higher exposure to risk due to lack of knowledge, (iv) vulnerability of the fetus49. Each of these may be due to lack of information that women can use to make decisions.

Women with a sick fetus may be at particular risk of “therapeutic misconception” (a bias towards wanting to help their fetus) so need information presented in a way that reflects their specific cognitive and emotional condition50. For example, some women who had participated in the ORACLE trial of antibiotics for preterm, prolonged rupture of membranes and were told of possible adverse results for women exposed to co-amoxiclav several years after they were recruited, felt guilt about their participation, while others remained happy with their involvment51.

On the basis of personal experience and the widespread unwillingness of institutions to support investigation of medicinal products in pregnant women we speculate that the risk of “therapeutic misconception” among families is mirrored by a risk of “ethical misconception” among ethical and legal reviewers. This “ethical misconception” may arise when the possibility of adverse outcomes clouds the ability of reviewers to focus on the possibility that research drug(s) under evaluation may provide significant benefit globally to pregnant women. Therapeutic misconception can be managed by context-specific information for families. Similarly, ethical misconceptions can be addressed with context-specific information for reviewers. This means better presentation of information and explicit justification of the clinical reasoning used in the situation that drives the research.

We believe that a clear view about how to handle many of these ethical issues is available but needs to be propagated. We suggest the following actions:

1. Improved presentation and uptake of the international consensus that research about new drugs used during pregnancy is appropriate and necessary
2. Clearer guidance about when and how to apply international consensus
   1. When standards can be used, when judgments are appropriate.
   2. Acceptance of diversity in practice, such as the need in countries such as the USA for biological fathers to give consent for some research during pregnancy – these countries cannot expect biological fathers to give consent in other countries.
3. Reducing uncertainty about safety by freely sharing information about the magnitude and nature of risks in a way that allows comparison with potential benefits
4. Share experience about how to handle ethical issues through case studies and formal research into communication, family perspectives and other key ethical concerns

Public-private partnerships that work across multiple drug development programmes would be well-placed to take these actions.

**FETUS AND NEONATE**

The central, and unique, problem for research in pregnancy is the need to account for the interests of two people: the mother and her offspring. This is difficult to consider, both emotionally and cognitively, unless you have experienced it as a parent or a carer. However, families and clinicians do this regularly in clinical practice. Many people approach the situation with a natural inclination to avoid harm to a fetus. However, in many clinical situations it is impossible to avoid harm – the harm has already happened. Pregnant women and fetuses are not excluded from clinical care because they may be “vulnerable”. This needs to be the starting point for the design and review of research about new drugs for pregnant women or the fetus. The conversation about research should not be made more difficult than the usual conversation related to the clinical problem that drives the research.

These principles need careful application given the wide range of potential treatments. Some treatments may be highly innovative and be difficult to assess safely in any population; examples being gene therapy and nanoparticle-targeted delivery of therapeutics. A patient-centred view is possible and can guide researchers52. Some of the uncertainty can be managed by careful surveillance with registries. A key question is who owns the risk? That is, who owns the adverse human outcomes and the benefits that actually happen? Who will suffer or benefit? We contend that well-informed families are best-positioned to inform discussions and about benefits and risks. The views of families should be the basis for judgments by ethics committees, regulators and other decision-makers. Long-term uncertainty is part and parcel of clinical care and is an important driver for research.

A key issue is how to assess benefits and harms. Currently, there is no consensus about when and how to follow-up high risk neonates. This is complicated by the evolving picture of outcomes – outcomes at discharge are frequently discordant at 5 years corrected gestational age53, 54. It is often not possible to give good answers about risks and benefits at the start of the study, or midway through it55. These uncertainties are not the result of research. These uncertainties are the clinical reality that families and clinicians deal with daily. Each study needs a plan for follow-up that takes account of outcomes that are predictable from the pharmacology of the new drug, and outcomes that are unexpected. This requires significant investment. Adaptive licensing may play a role in addressing these uncertainties during the evaluation of new drugs56. The neonatal community is grappling with these issues so that collaboration between the communities is essential.

**SOLUTIONS**

Activities in single programmes and for the community are summarised and compared in Figure 1. These activities cannot be done in isolation. We need to take a systems approach to address “all layers of the onion” that is illustrated in Figure 2.

*Steps for single programmes***.**

Programmes and individual trials should involve a broad study team with all relevant disciplines and include potential participants (or their advocates). Steps towards designing clinical trials are summarised in Table 3. Aspects that are specific to pregnancy include:

1. Identify which data is needed for design and review of the trial. For example, FDA review of a clinical programme or study requires information about non-clinical safety, a case series if the drug has been used off-label, information about epidemiology, and information that supports efficacy. This information needs to be gathered prospectively in a manner that informs decisions about clinical studies and in a form that can be submitted to regulatory agencies.
2. Identify information about the context that is needed to inform trial design and review. This includes information about the ethical, legal and social features of the specific condition and population under study.
3. Consider multiple perspectives when preparing for judgments. Contributors such as investigators or regulators needs to reach out to others, and pay attention to what others say. This needs to be anticipated as information is gathered.
4. Consider whether judgments are similar to judgments made between families and clinicians in clinical practice (which may include comparing apples with oranges)55, or whether another style of judgment is needed. State the basis for judgments that is used. For example, the basis for judgments in the following three scenarios is different:
   * 1. Single-dose study of maternal vitamins (discussed at 36 weeks gestation)
     2. PK study of a drug intended to delay preterm birth (discussed during preterm labour at 26 weeks)
     3. Proof-of-concept study of a drug intended to ameliorate congenital diaphragmatic hernias (discussed at diagnosis at 21 weeks)
5. IRBs need to consider the relevant style of judgment (is it internally consistent and societally appropriate) and have the appropriately broad expertise to do so.
6. Make skilled judgments based on:
   * 1. Ability to make judgments and stick with them.
     2. Awareness of limits of what can be tolerated by stakeholders – including study participants in the light of their clinical condition and its natural history – and the consequences of crossing the limits
     3. Trade-offs between likely benefits and likely burdens and harms, taking account of the impact and consequences of crossing any stakeholders’ limits.

Steps 1 – 6 depend on pregnancy-specific information that may not be collected in “standard” approaches to drug development

1. Dosage Regimen
   1. Overcome lack of understanding of pharmacokinetics (PK) and data-driven dosing. A systematic review found a total of 198 studies involving 121 different medications57. PK studies during pregnancy are possible but have only scratched the surface of information required for rational prescribing during pregnancy.
   2. Consider PBPK models22
2. Trial supplies

Excipients (non-active components of the pharmaceutical preparation) are important. In other populations, excipient selection can be based on whether a substance is “generally regarded as safe” but this is not a safe approach during pregnancy 58 Nanoparticles and other novel excipients need dedicated assessment if they are to be used during pregnancy.

1. Recruitment

As noted above, recruitment should be based on a trial-specific and patient-centred approach to education about trial features, especially safety59, that is designed for each study.

1. Developing, agreeing and adhering to core data sets and shared outcomes thatwill allow comparison of data arising from multiple trials and better facilitate individual patient data metaanlayses.

*Community*

Many of the challenges that arise during the evaluation of new drugs that used during pregnancy can only be addressed by a community made up of multiple disciplines and perspectives. The actions needed to promote maternal and neonatal health care that are needed in low and middle-income countries have been described60. See Table 4.

The materno-fetal community is trying to build a community through the Global Obstetrics Network, GONet <http://www.globalobstetricsnetwork.org> and this academic initiative is an ideal basis for the development of a private public partnership that includes PlaNet16.

The report by PRGLAC to the US HHS includes some recommendations that can form the basis for influencing policies ([https://www.nichd.nih.gov/sites/default/files/2018-08/TaskForce\_MeetingSummary4.pdf](https://urldefense.proofpoint.com/v2/url?u=https-3A__www.nichd.nih.gov_sites_default_files_2018-2D08_TaskForce-5FMeetingSummary4.pdf&d=DwMGaQ&c=ZbgFmJjg4pdtrnL2HUJUDw&r=JkHnUDF4nk8U6KqghGW_umYQwlw6Fk-LmpZMUpxEzwjYBB8uFEv7VZDXRAJ4xaKx&m=Or_rHw5fj36ndZD9JcPsRO-Kz7_qHMYqD6MDMRdKYwg&s=FYSVxKYM_QRkr6WgKbiyJYJ26Z1P7mHOHaf5nANW9sM&e=)), including:

* Remove pregnant women as an example of a vulnerable population in the Common Rule and FDA regulations
* Provide more resources for research (money, human and infrastructure)
* Ensure that only one parental signature is required for research during pregnancy
* Implement a liability-mitigation strategy for conducting research and evaluating new therapeutic products in pregnant women and lactating women
* Drive discovery and development for new therapies in high priority conditions
* Develop programmes to study off-patent products used during pregnancy, similar to the programmes for products used in children
* Proactive approach to the inclusion of pregnant women in research
* Leverage established and support new infrastructures/collaborations to perform research in pregnant women and lactating women

The US community needs to influence Congress to pass the necessary legislation.

Advances in the US are an opportunity for the materno-fetal community outside the US to promote these ideas.

*Comparisons with other communities*

In pediatrics significant investment has been made through legislation, policy and infrastructure over several decades3, 7 based on leadership from each stakeholder focused on the needs of the community.

The International Neonatal Consortium (INC) is a precompetitive public-private partnership that has published several documents that clarify neonatal drug development 61 62 63 64 Efficient public-private partnerships need to be well-targeted with professional management of expectations and high-quality facilitation65. The clinical community and its learned societies need to promote regulatory, legal and ethical changes66.

Additional investment in pediatric research infrastructure includes the setup of FDA-funded research networks led by the Insititute for Advanced Clinical Trials (iACT, https://www.iactc.org) and the Duke Clinical Research Institute (https://dcri.org/global-pediatric-clinical-trials-network/) in 2017 and the European Innovative Medicine Initiative 2 (IMI-2) / European Federation of Pharmaceutical and Industries Association (EFPIA) co-funded network Conect4Children (c4c, https://conect4children.org) that was initiated in 2018.

We note that there has been progress in other aspects of Women’s Health when appropriate investment has been made in “multipronged” approaches, including attention to study design, communication, and policy initiatives67. Another example comes from the neglected disease community68

**CONCLUSIONS**

This review has described some ways to address the challenges that arise when testing new drugs that could be used during pregnancy. We have emphasized a multi-levelled approach needed to overcome these challenges.

Individual drug development programmes need to gather a body of scientific and clinical information with drug development in mind. This requires a focus on regulatory pathways. Additional information is needed to support the judgments about benefits and risks related to trials made by study teams, Sponsors, regulators, ethicists, and, above all, families who will decide whether or not to participate in a trial. As this additional information has not emerged from research to date, researchers and the community need to develop strategies for information gathering that will supplement their current approaches.

Over the past decade there have been many calls for the materno-fetal community to develop new drugs for pregnant women and fetuses. To do this, the community must develop a global public-private partnership and identify actions to take as a community. The mother and fetus, true drug orphans of the 21st century, urgently need us to deliver on these action plans.

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Table 1. Overview of strategies and challenges (other than funding)

|  |  |  |
| --- | --- | --- |
| Strategy | Challenges (other than funding) | Solution |
| Models |  |  |
| * Placental transfer * Impact on fetus (teratogenesis) | Identification  Validation and Qualification  Animals  Application of existing physiologically-based pharmacokinetic (PBPK) models | Science targeted at drug development  Understanding of regulatory issues  Understanding of relevance  Dissemination of existing knowledge |
| Novel approaches to regulatory issues | Consensus, combined with working understanding of diversity | Pre-competitive regulatory agreement, taking account of uncertainty |
| Funded Registries | Design, including real world data  Design: specific times / specific drugs | Focused methodologies  Data quality  Data standards  Possible, but need some work  Setup and run |
| Maternity Investigation Plan | Concept  Adoption  Enforcement (requirement) | Describe  Educate  Advocate |
| Involvement and Engagement | Communication  Partnership | Contacts and Trust developed through honest broker third parties |

Table 2. Funding Challenges and Solutions

|  |  |  |
| --- | --- | --- |
| Challenges | Solution | |
|  |  | Public –private partnerships |
| Describing costs and benefits | Targeted gathering of information |
| Comparing options | Develop methodologies for comparisons |
| Building a market for research | Relevant incentives for all contributors to the research process |
| Building a market for drugs | Access to new medicines, improve implementation of new interventions |
| Comparing moral arguments to economic arguments | Policy advocacy |
| Political awareness | Coordinated campaign free from conflicts of interest |

Table 3. Steps for individual clinical drug development programmes.

See text for pregnancy-specific details

|  |  |
| --- | --- |
| Generate information needed for judgments about the design of the programme / study | |
|  | Identify which judgments are needed: |
|  | * Study design by Sponsor and Investigators |
|  | * By families approached about recruitment |
|  | * Review by ethics and regulators |
|  | Identify information about the context that is needed to inform trial design and review. |
|  | Consider how to minimise harm while optimising likelihood of identifying a reliable signal for efficacy (or the lack of an effect) – what is the factual basis for trade-offs? |
|  | Consider multiple perspectives when preparing for judgments. |
| Identify options for key design features | |
|  | Eligibility |
|  | Outcomes: identify clinically important or validated / qualified surrogate |
|  | Interventions: nature and dosage (see below) |
|  | Invasiveness of assessments |
|  | Harms from the trial |
|  | Direct benefit or not |
|  | Minimal harm or not – justifications, not assertions |
| Judgments about safety and efficacy – using information to select between options. | |
|  | Consider whether judgments are similar to judgments made between families and clinicians in clinical practice |
|  | Consider precedents and guidelines taking account of the context, the intervention, and similarity to the current situation. |
| Plan | |
|  | Preparedness of clinical studies, including site-level feasibility |
|  | Consider studies that test procedures and assumptions about recruitment (in silico M&S, in vivo trial simulation, pilot trials) |
| Dosage Regimen | |
|  | Overcome lack of understanding of PK |
| Trial supplies | |
|  | Active Pharmaceutical Ingredient |
|  | Excipients and Formulations |
| Approvals | |
| Recruitment | |

Table 4. Steps for the materno-fetal community.

The materno-fetal community refers to all groups and individuals that contribute to the design, review, implementation and use of research about drugs used to treat maternal or fetal conditions during pregnancy.

| Steps | Actions |
| --- | --- |
| General | |
| Recognize the stakeholders as a community | Open and transparent recognition of the value of many perspectives  Integrate multiple perspectives into a tractable vision and mission, and community of practice |
| Build a Coalition | Develop informal and informal groups in appropriate geographical and methodological settings, with global coordination |
| Policy development (context specific) | Prioritise and form appropriate, pan-stakeholder groups. |
|  |  |
| Specific | |
| Identify therapeutic needs | Epidemiology, burden, ethical, legal and social contexts |
| Facilitate data sharing (before and after licensing) | Data standards  Governance for data sharing  Facilities for data sharing |
| Promote proportional review (legal, ethical and regulatory) | Identify key features of important clinical situations that should guide the design and review of programmes and individual studies – including consistent interpretation of regulatory and legal texts, and identification of useful precedents |
| Pre-competitive collaboration on methodology development and refinement | Prioritise and form appropriate, pan-stakeholder groups. |
| Lobby for equity between pregnancy and other populations | Resources for medicines  Access to medicines |
| Develop and promote guidelines for research design, review, and conduct | Prioritise and form appropriate, pan-stakeholder groups. |
| Implement innovations efficiently | Develop effective links with relevant communities and use good implementation science / knowledge exchange strategies |
| Reconcile with broader societal considerations | Recognise competing priorities and make a strong case for drug development in pregnancy |