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The Research Cycle: Improving Care and Outcomes for Newborn Infants

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Abstract
Ensuring that policies and practice in perinatal care are informed by evidence from high-quality research is fundamental to improving outcomes for newborn infants and their families. Effective interventions in the perinatal period can have a life-long impact disproportionate to their costs. Many of the major advances in care that have transformed outcomes for preterm and sick newborn infants have been informed by empirical and applied health research. Conversely, there are examples of life-long adverse consequences for infants and families that are a legacy of practices based on poor-quality evidence. The challenge in the 21st century is to maintain the trajectory of improvements in care and outcomes. This will most likely be achieved via marginal gains from new or improved care practices underpinned by a range of research approaches, from preclinical and laboratory-based empirical studies that uncover pathogenic pathways or therapeutic mechanisms, to large-scale, applied research such as multicentre, randomised controlled trials. This will involve the coordination and collaboration of research efforts globally. Strategies to develop and prioritise research questions need to involve parents and families. Given the context in which much perinatal research is conducted, particularly in emergency situations around the time of birth, robust and transparent ethics and governance frameworks are essential to maintain the trust and engagement of communities. An ethical imperative exists to ensure that research output is disseminated effectively, and that effective and cost-effective interventions are implemented and integrated within a cycle that audits and benchmarks good practice and outcomes, and informs research evidence-based continuous quality improvement. This is the first in a series of articles on research methodology in neonatal medicine to be published in *Neonatology*, in response to a request from trainee researchers. We introduce the series by describing the research cycle, in particular how it is applied in neonatal medicine. Subsequent articles will cover translational research, clinical trials, diagnostic tests, global challenges, and the ethical issues relating to neonatal/perinatal research.

This paper is the first article of the special series "Research Methods in Neonatal Medicine" (Guest Editor: Bill McGuire, York, UK).

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Most things we do in medicine have no (direct) supporting evidence that they do more good than harm.
William A. Silverman

Introduction

Bill Silverman's call [1] to base our care practices on the best evidence from high-quality research remains relevant today. Having made major advances in perinatal care over the past 5 decades, the ongoing challenge is to undertake high-quality research to address the gaps in our knowledge about the persistent and emerging causes of morbidity and mortality of newborn infants [2, 3]. Over the next year, *Neonatology* is publishing a series of commissioned articles on this theme, and Bill McGuire will act as Guest Editor for these important papers. They will be written by clinicians and methodologists with experience and expertise in perinatal research. They will describe key aspects of research design and governance, and discuss strategies for undertaking valid and impactful research in a variety of health care settings. This is the first of these articles and it describes the research cycle.

The Research Cycle

Policy and practice should be informed by the best-quality (and least-biased) research evidence available. "Research," defined broadly, encompasses a range of activities that can contribute to improvements in care and outcomes. These include "preclinical" laboratory-based studies, "clinical" observational and experimental studies, qualitative evaluations of family and care-provider views, economic analyses to provide context to health services with finite resources, and quality improvement programmes incorporating audit and benchmarking cycles within clinical networks. These activities are inter-dependent and form the "research cycle" (Fig. 1), which integrates the development, evaluation, and adoption of better tests and treatments, with health care and service needs, and infant and family views and expectations.

The identification of research needs, the prioritisation of research questions, and the development of research strategies start with the recognition of clinical concerns or problems. Research may be triggered, for example, by an awareness of gaps in our knowledge about a common cause of mortality or morbidity (such as necrotising enterocolitis), or by demonstrating unexplained variations in outcomes between centres (e.g., the rates of surgery for necrotising enterocolitis). These observations may be at the local level, or at a regional or national level, and they may trigger various types of research activity.

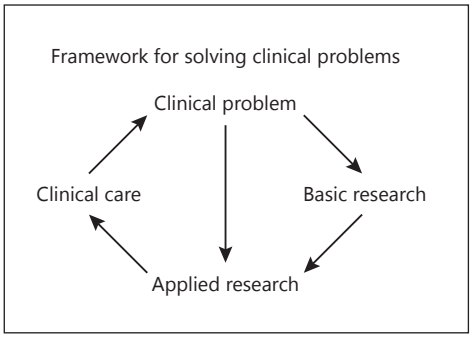

Fig. 1. The research cycle.

At the outset, all research, including preclinical or clinical studies, should be underpinned by a systematic review of the existing evidence in order to avoid the research waste, and by an evaluation of parent and care-provider views on important questions and outcomes [4, 5]. Ultimately, the hope is that research contributes to the development of better treatments or tests or prognostic information. New interventions can then be evaluated in large-scale studies, ideally in "real world" settings and conditions. If they are shown to be clinically effective and cost-effective, they can be adopted as standards of care to improve outcomes for infants and their families.

Early-Stage Translational Research

Preclinical (sometimes referred to as "basic") research has underpinned many of the advances in care that have transformed outcomes for newborn infants [6]. Research studies using biochemical, physiological, or molecular genetic techniques, and cell culture or experimental animal models, have informed, for example, the development of antenatal corticosteroid therapy, exogenous surfactant administration, nitric oxide treatment for respiratory failure, and therapeutic hypothermia for neonatal encephalopathy [7–10].

Early-stage translational research is the topic of the next article in this series. The authors will discuss the ongoing role of preclinical studies in the 21st century, and describe how "blue-sky" and inter-disciplinary preclinical research

remain key to improving our understanding of the pathways leading to disease in newborn infants, and can be the starting point for the development of new interventions and tests to improve neonatal care and outcomes.

Clinical Studies and Trials

A variety of clinical research study designs exist. Broadly, these are categorised as "observational" or "experimental." Commonly used observational designs include cross-sectional, case-control, and cohort (retrospective or prospective) studies. These design frameworks can be adapted to address a range of questions, such as etio-pathogenesis (including genetic risk factors), safety, diagnostic accuracy, and prognosis (studies of which can extend for the life-course and across generations). These descriptive and exploratory approaches are particularly useful for studying rare conditions or outcomes that are uncommon. For example, cohort and case-control studies provided the first indications that exposure to antenatal magnesium sulfate was associated with a reduced risk of cerebral palsy in very-low-birthweight infants [11, 12].

While observational studies can reveal associations, however, they are generally not suitable for demonstrating causality, because confounding factors can contribute to the associations observed. Experimental studies are less subject to confounding and other sources of biases that skew estimates of effect [13]. The randomised controlled trial (RCT) is the optimal design for determining efficacy and effectiveness, provided it is large enough to detect important effect sizes [14]. For example, prompted by the observed association of antenatal magnesium sulfate with a lower risk of cerebral palsy, clinical investigators, internationally, undertook RCTs to provide causal evidence of the neuro-protective effects of magnesium in very-low-birth-weight infants [15].

The third article in this series will describe the central role of clinical trials in perinatal research, with an emphasis on developments during the past 10 years, particularly the use of simple and pragmatic designs to undertake the large, multicentre RCTs needed to assess outcomes that are important for the infants and their families [16]. The authors will discuss developments in efficient trial designs, including the use of routinely collected outcome data. These approaches are likely to be increasingly common as we seek to undertake the very large trials that are needed to detect marginal improvements in care and outcomes that can, in turn, affect life-long outcomes for newborn infants and families [17].

Assessing Diagnostic Test Accuracy

The assessment of the accuracy of diagnostic tests, even those commonly used, remains a poorly understood and somewhat neglected area of clinical research. However, the appropriate use of tests, informed by high-quality (unbiased) evaluations of their accuracy (their ability to predict outcomes), is an essential component of evidence-based practice. For example, studies of the accuracy of oxygen saturation measurement for diagnosing congenital heart disease have had a major impact on care pathways and infant outcomes [18]. Other areas of active research interest in neonatal care include the accuracy of biomarkers for diagnosing invasive infection, and the comparative accuracy and utility of neuro-imaging modalities in predicting neurological or developmental outcomes in very preterm infants [19, 20].

The assessment and application of diagnostic test accuracy will be explored in the fourth article in this series. The authors will provide a methodological overview for clinicians about what makes a good diagnostic test, how research studies should assess accuracy, and how clinicians should appraise and apply the research evidence on diagnostic test accuracy and utility.

Integrating Parents and Families in Research Initiatives

Research funders increasingly require evidence of parental involvement and shared decision-making in developing research questions, particularly in the choice of outcome measures important for infants and their families. Priority topics for publically funded research should be developed by collaborations of clinicians, care providers, service commissioners, and infant- and family-advocacy organisations [4]. The aim is to ensure that proposed research is likely to be acceptable and feasible, and that research outputs meet the needs of service users and service providers. "Priority-setting partnerships" of service users and service providers can inform research agendas by identifying important gaps in knowledge and evidence by means of surveys and systematic reviews of existing studies and guidelines [5].

The fifth article of this series will describe the opportunities and challenges surrounding parental involvement in research, and its importance at all stages of the research cycle, from the formulation of questions to the dissemination and implementation of findings.

Global Challenges for Perinatal Health Research

Despite improvements in perinatal care and outcomes during the past 2 decades, 2.6 million newborn infants die each year, predominantly in south Asia and central and sub-Saharan Africa. Most neonatal deaths are due to complications related to preterm birth and low birth weight, or adverse intrapartum events, and occur at home or in low-technology health care facilities [21]. While enormous challenges exist for developing and implementing sustainable interventions to address this burden in low-income countries, notable advances have been made in some areas such as the reduction in global mortality from neonatal tetanus [22]. Priority areas for research to further reduce perinatal mortality and morbidity globally include interventions to promote skilled care during labour and childbirth (at both health care facilities and at home), reduce the risk of infection associated with umbilical cord care, support breastfeeding and "kangaroo mother care," and improve the recognition and treatment of neonatal infections [23]. While the focus is on community-based interventions, research is also needed to evaluate and improve the safety and effectiveness of interventions used in health care facilities and integrated local "health systems" [24]. Much of the currently available evidence for facility-based neonatal care is from studies undertaken in high-income countries, and much of it is not directly applicable in resource-limited settings. There is a need to scale-up research efforts to include large, pragmatic clinical trials to assess the effectiveness, relevant to the setting and in terms of costs, of many of the routinely used interventions in resource-limited settings, particularly in sub-Saharan Africa [25].

The sixth article of this series will consider the opportunities and challenges of conducting large-scale research studies in low-to-middle-income countries, discussing both health care facility-based and community-based initiatives, and describing the areas for evaluation and implementation that align with research priorities.

Ethics of Perinatal Research Participation

The critical importance of robust ethical governance in all research cannot be overstated. Safety and respect for the rights of study participants is fundamental to good research. Studies that are designed/conducted badly are unethical, even if they do not place participants at direct risk or harm, because people agree to take part in studies on the premise that the design is fit-for-purpose. Frameworks for ensuring rigorous ethics in perinatal research are well-established in many countries, and are integrated into research prioritisation, funding, and approval pathways. Perinatal research, however, does bring with it additional complexity, particularly with regard to consent, because permission for infants to participate in studies is typically provided by parents [26]. This issue is especially difficult when considering interventional research in the emergency care setting, for example immediately after birth [27]. Various approaches to ensuring that parents are fully informed and can actively give permission for infants to participate in research have been considered and assessed, but there is uncertainty and the debate about how to best integrate these processes in pragmatic studies is ongoing [28].

The authors of the seventh article of this series will provide a practical overview of research ethics for clinicians (in various settings), discussing the principles of informed consent and the roles that the various governance and regulatory frameworks play in ensuring quality and ethical rigour in research studies.

Evidence into Policy and Practice

Completing the research cycle requires that we ensure that what is implemented in practice is based on findings (or that ineffective interventions are removed from practice), and that there is equity of access to effective and cost-effective interventions. In perinatal health care settings, this is increasingly facilitated by audit, benchmarking, and quality improvement activities embedded in the regional, national, or international networks of neonatal units [29]. These facilitate the monitoring and peer-referencing of care practices and risk-adjusted outcomes. The aim is to highlight excellence, so that centres may identify areas of good practice that they wish to adopt or adapt from within their network. For example, continuous quality improvement projects have been used to promote the use of evidence-based interventions to reduce the risk of nosocomial infections

in neonatal units, and to decrease in the incidence of hypothermia in very-low-birth-weight infants in the delivery room [30, 31].

The eighth article in the series will describe how multifaceted quality improvement initiatives can be coupled with research, aiming to improve performance, professional development, policies and practice, and ultimately infant and family outcomes [32].

What Makes Good Quality Research Evidence?

The concluding article will summarise some of the key lessons and messages from the series, and discuss current approaches for appraising the quality of research and research outputs so that these may be valid and useful for clinicians, families, and guideline writers and service commissioners [33]. We will highlight the role of research synthesis in this process, and the contribution of the Cochrane and systematic reviews to improving the conduct and reporting of primary research studies.

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