**Regulatory Science in Neonates: a framework that supports Evidence-based Drug Therapy**

Mark A. Turner MBChB, PhD1,2\*

Ronald J. Portman MD1,3

Jonathan M. Davis MD1,4

 1Co-Director, International Neonatal Consortium

2 Institute of Translational Medicine, University of Liverpool , Liverpool, UK

3 Executive Director, Pediatric Therapeutic Area, Novartis Pharmaceuticals, East Hanover, NJ USA

 4Tufts Medical Center and the Tufts Clinical and Translational Science Institute, Boston, MA USA

\*Correspondence to Dr. Turner

Mark A. Turner

Neonatal Unit

Liverpool Women’s Hospital

Crown Street

Liverpool

L8 7SS

UK

Phone: +44-151-795-9555

Fax: +44-151-795-9599

mark.turner@liverpool.ac.uk

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**Introduction**

The International Neonatal Consortium (INC) integrates global stakeholders to promote clinical drug development for neonates1. INC focuses on generalizable methods for using data to support claims that a drug is safe and efficacious when used to treat a specific indication (regulatory science).

The framework provided by regulatory science has many similarities with evidence-based medicine including a “gold standard” approach of more than one adequately powered randomised controlled trial when possible. Regulatory science includes several steps not usually emphasized in evidence-based medicine, including: pre-clinical studies of toxicology and effects; optimised drug formulations; transparent justification of dosage and trial design; a series of studies (including Phase 1 and 2 studies, so-called therapeutic exploratory studies) that are used to design the pivotal randomized clinical trials (RCTs) (so-called therapeutic confirmatory studies)2. These steps promote the success of large RCTs while derisking the large RCTs for patients, funders and investigators. Regulatory science includes a framework when large RCTs are not feasible3. The information generated by applying regulatory science supports judgments about drugs and biologics, typically to allow a product to be placed on the market and support rational use of the marketed drug. An adapted regulatory science framework can also support the use of drugs if they need to be used off-label.

Contemporary regulatory science emphasizes: 1) a programme based on systematic synthesis of data from preclinical and clinical sources, rather than a series of uncoordinated trials; 2) study designs that are based on data about natural history and patient flow, rather than expert opinion; 3) explicit understanding of the performance of biomarkers and surrogate outcomes; 4) the voices of patients and their families; 5) real-world data when appropriate, taking into account the need for shared definitions, interoperable data systems and trade-offs with data reliability, control of errors, study size and safety4.

In order to advance the paediatric community’s understanding of regulatory science, we highlight two domains: collection of high quality data and the rational use of data. High quality data involves reliable measurements with acceptable inter- and intra-observer variation, not necessarily the measurements used in clinical practice or collected in existing databases. Additionally, quality involves paying close attention to how the data are collected, including checks on data entry (monitoring). The second domain concerns the rational use of information during clinical drug development. This involves a number of components: 1) quantitative models for the effects of the drug based on prior knowledge about natural history of the condition; 2) analysis of pharmacokinetics that can come from other age groups or animals through extrapolation; 3) demonstration of safety including pre-clinical toxicology studies and phase I studies in a small number of patients; 4) predictions about the expected effect size; 5) identify gaps in the models that need more information; 6) gather data that will improve the model and the predictions (e.g. conduct a large RCT or alternatives such as adaptive designs); 7) use the data to test the model and the predictions (did the effect size in the RCT match what was expected); 8) validate predictions in independent cohorts (e.g. do more than one large RCT when possible); 9) apply understanding to the clinical situation3. Ideally, steps 2 – 8 are performed more than once.

Figure 1 is a qualitative scheme for classifying limitations in neonatal drug development according to whether there is sufficient data or sufficient understanding of extant data to develop a new or existing drug for the condition. We apply this scheme to three therapeutic areas in order to assess the next steps for these priority conditionss.

*Infection*

Bacterial infections, or suspected infections, are common in neonates. The effectiveness of antibiotics can be assumed based on animal and adult human studies but the neonatal evidence base for antibiotics is limited, particularly for multiple drug resistant bacteria. The biggest challenge in neonatal antibacterial drug development is our limited understanding of the penetration and efficacy of antibiotics into the central nervous system (CNS). This can be addressed by measuring CNS penetration in animals before conducting bridging studies to estimate pharmacokinetics and pharmacodynamics in neonates5,6. This results in the placement of neonatal infection predominantly in Quadrant B. The priority for infection is to gather data to define the penetration and effects of antibiotics, particularly in the cerebrospinal fluid.

*Retinopathy of prematurity (ROP)*

Novartis is conducting the 32-country RAINBOW study to evaluate the efficacy and safety of two doses of the vascular endothelial cell growth factor (VEGF)-inhibitor RAnibizumab (Lucentis) compared with laser therapy for the treatment of INfants BOrn prematurely With retinopathy of prematurity (NCT02375971) Shire investigated the continuous infusion of recombinant IGF-1 (rhIGF) and its binding protein, IGF binding protein-3 (rhIGFBP) for the prevention of ROP in a Phase 2 exploratory study (NCT01096784). There is a need for consistency between these programmes and future work. High quality data collection and data analyses are underway. ROP is an example of a program placed in Quadrant C in Figure 1. The main need for regulatory science is the development of elements for common protocols including an updated classification of ROP as a robust and clinically relevant outcome measure required for regulatory decsision-making7.

*Haemodynamics*

The assessment of neonatal circulation relies mostly on arbitrary thresholds that have been the subject of debate for decades. Before drugs for blood pressure or other conditions can be evaluated, there is a need to justify thresholds for inclusion criteria with parameters such as blood pressure. The current knowledge gap in neonatal hemodynamics would be allocated to Quadrant D in figure 1. That is, methods to collect high quality data need to be determined and, key definitions need to be developed in order to use that high quality data more effectively.

**Discussion**

There is diversity between neonatal therapeutic areas with some areas having high quality data, but lacking a framework for evaluating drugs. Others areas lack any useable data at all. INC has developed a novel approach to needs assessment in regulatory science and is currently addressing these needs. Regulatory science may be relevant to other pediatric populations as a supplement to evidence-based medicine.

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Figure 1.

Title: A scheme for Regulatory Science

Legend:

The Figure shows a qualitative scheme for classifying limitations in neonatal drug development according to the extent of data that is available, or the extent of understanding about the condition under study.

Quadrant A is the ideal case in which preparatory work has identified high quality data and a logical chain of argument to support the development of a drug.

In Quadrant B there is sufficient understanding of the clinical situation to develop a rational framework but more information is needed – for example to confirm the predictions made using information about natural history, extant data from trials or well-designed registries or to apply established biomarkers.

In Quadrant C there is high quality data but it is not clear how the data support a drug development plan – for example high quality registries and/or systematic reviews are available but have not been collated in a way that informs regulatory decisions or biomarkers have not been validated.

Quadrant D represents a lack of knowledge and a lack of understanding. In this case effort is needed to gather information about natural history, validate biomarkers, define formulations and dosage before planning a series of clinical trials