Imperial College London

Chelsea and Westminster Hospital NHS
NHS Foundation Trust

Principles of embedding clinical trials (and other research) in neonatal care

Neena Modi
Professor of Neonatal Medicine
Imperial College London

@NeenaModi1
n.modi@imperial.ac.uk

NDAU
Neonatal Data Analysis Unit

UK Neonatal Collaborative

- The ethical case for embedding research and evaluation (not just trials) into everyday clinical care
- Creating the infrastructure
- An example of an embedded trial
- Professional and parent buy-in
- Future directions

The ethical case

A large amount of what we teach and learn is wrong; a large number of treatments are unproven

Lack of research is a patient safety issue

- Thymic irradiation of neonates = 5-fold increase in cancer
- Placing babies prone to sleep = greater risk of sudden death
- Routine separation of mothers and babies = decreased breastfeeding
- 100% O2 resuscitation = 3-fold mortality increase compared to air
- Antenatal steroids in low income countries = greater neonatal mortality

All once considered standard of care!

A positive approach to research:
Randomisation as the default and a standard of care for comparative effectiveness evaluations

- "Treatment A and treatment B are used by doctors everyday; we want to give your baby, and every other baby the best treatment, but we do not know which this is"
- As we do not know which is best, we will give every baby an equal chance of getting the best treatment (this is called randomisation); we will then be able to find out which is better
- If we don't do this we will never find out which treatment is better and many babies will continue to receive the wrong treatment
- You are free to opt-out if you wish

This is ethically valid

- **Justice:** the patient is treated fairly
- **Beneficence:** the doctor fulfils his/her obligation to act in the patient's best interests
- **Non-maleficence:** the doctor fulfils his/her obligation to do no harm
- **Autonomy:** the parent can opt-out, freely and without coercion

Research ethics committee decision-making in relation to an efficient neonatal trial

C Gale, M J Hyde, N Modi, on behalf of the WHEAT trial development group

Arch Dis Child Fetal Neonatal Ed 2017; 102:F291-F298

OPEN ACCESS

Section of Neonatal Medicine, Department of Medicine, Imperial College London, Chelsea and Westminster Hospital Campus, London, UK

Correspondence to
Professor N Modi, Section of Neonatal Medicine, Department of Medicine, Imperial College London, Chelsea and Westminster Hospital Campus, 369 Fulham Road, London SW10 9NH, UK;
n.modi@imperial.ac.uk

CG and MJH contributed equally.

- With the support of the UK Health Research Authority we tested 4 principles for application in comparative effectiveness trials:
  - Trial data from routine electronic patient records
  - Simple, short information sheet
  - Opt-out consent
  - Explicit mention of possible inclusion benefit

What this study adds?

- The UK Research Ethics Committees find the use of electronic patient records, short participant information sheets and mention of inclusion benefit to be acceptable in neonatal comparative effectiveness research.
- There is inconsistency between the UK Research Ethics Committees in relation to the validity of opt-out consent processes for neonatal comparative effectiveness research.
- The wider application of these methods may facilitate larger, more efficient randomised controlled trials.

- The UK Health Research Authority now accepts all 4 principles including opt-out and has issued guidance to all REC

Infrastructure

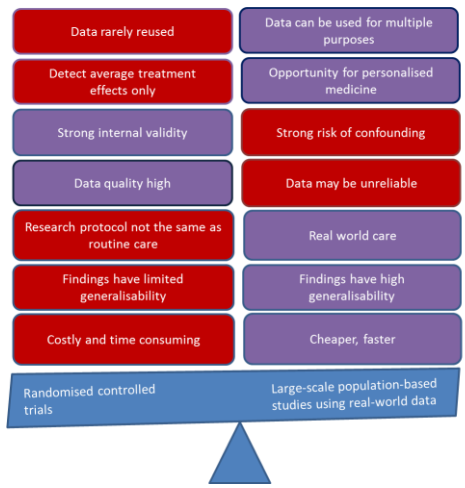
Real-world data
to develop and deliver more efficient studies

Baseline event rates	Often wrong
Eligible patient numbers	Often unknown
Recruitment rate	Often unrealistic
Parent support	Often lacking
Professional buy-in	Often uncertain
Local knowledge	Often lacking
Cost	High
Burden	High
Duration	Long

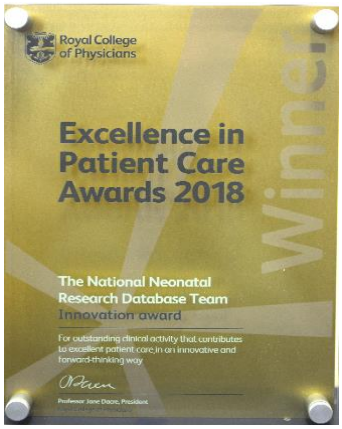
Conventional clinical trials

- Slow
- Stand-alone, separate from clinical care
- Data neither shared or reused
- Expensive
- Burdensome
- Rigid
- High internal but poor external validity
- Identify only average treatment effects
- Too often inconclusive

The advantages of Real-World Data



Beyond embedded trials
A proven model of real-world health data to improve patient care: the UK National Neonatal Research Database



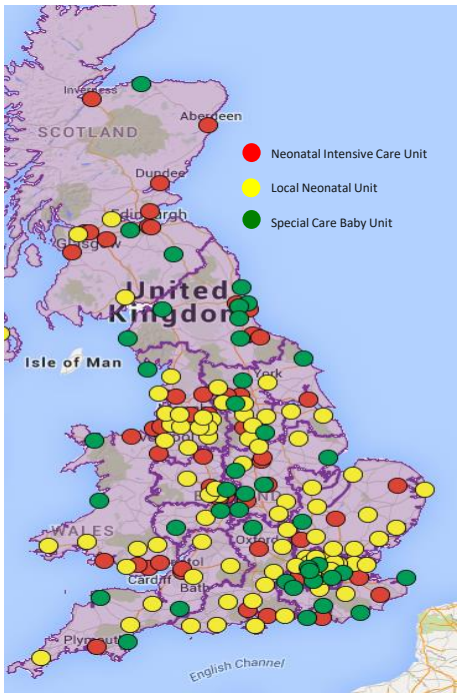
UK National Neonatal Research Database

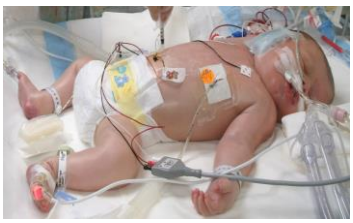
Imperial College London

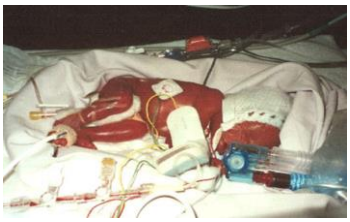
Established 2007; to-date contains data on over 1 million infants; 100000 new patients added annually;

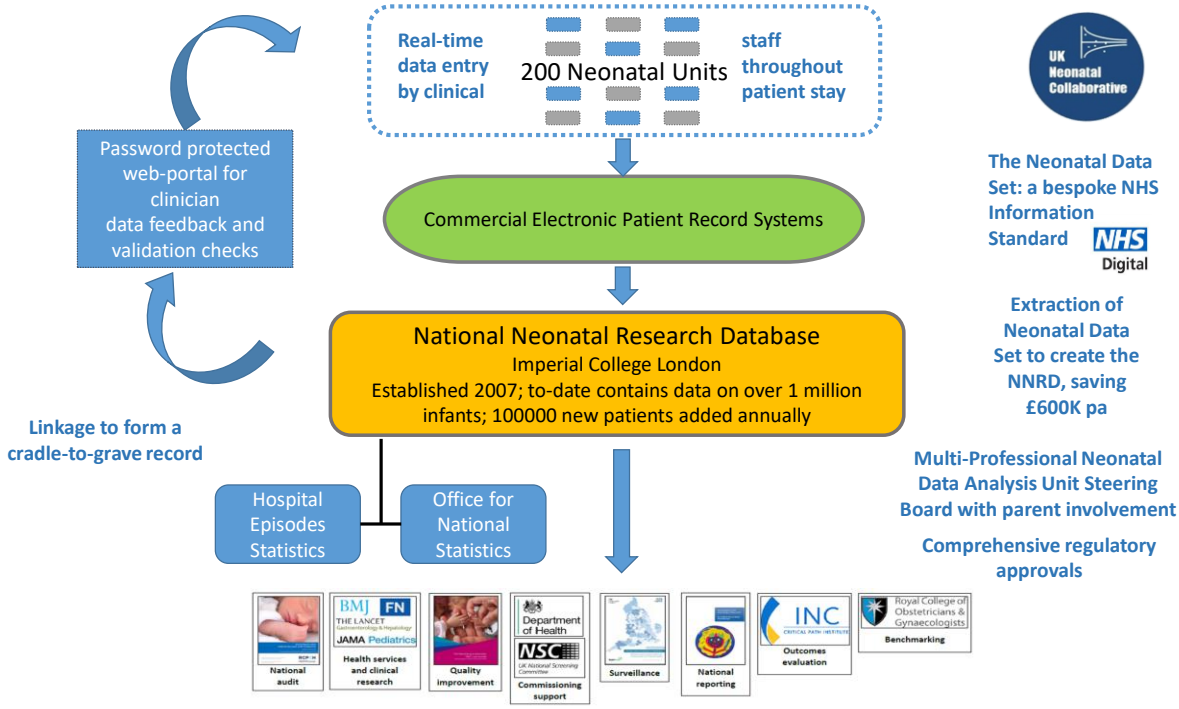
unique in having complete population coverage

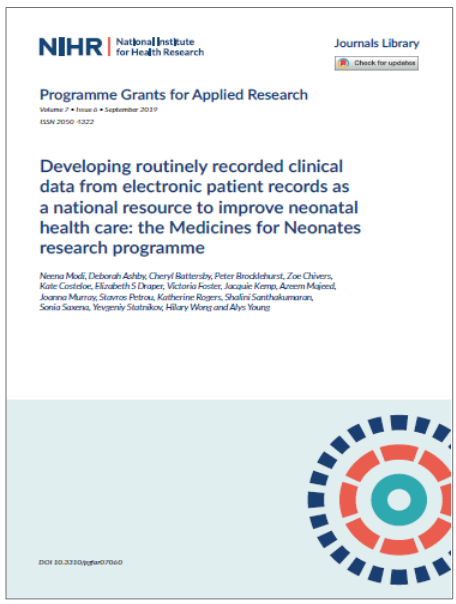
- Created from routine electronic patient records
- Used for multiple purposes
- Recognises the principle that data should be recorded once, and quality assured
- All stakeholders should be involved in developing the wider secondary uses of healthcare data











https://www.journalslibrary.nihr.ac.uk/pgfar/pgfar07060

A randomised registry trial in practice

WitHolding Enteral feeds Around blood Transfusion in neonates (WHEAT)

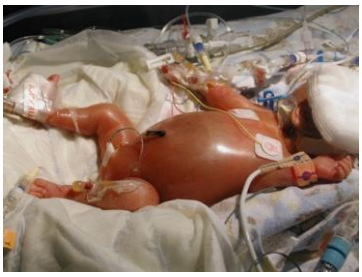
A Proof-of-Concept Point-of-Care Randomised Registry Trial (Chief Investigator: Chris Gale)

P: In babies born at <30+0 weeks gestation

I: Does omitting enteral feeds before, during and after blood transfusion

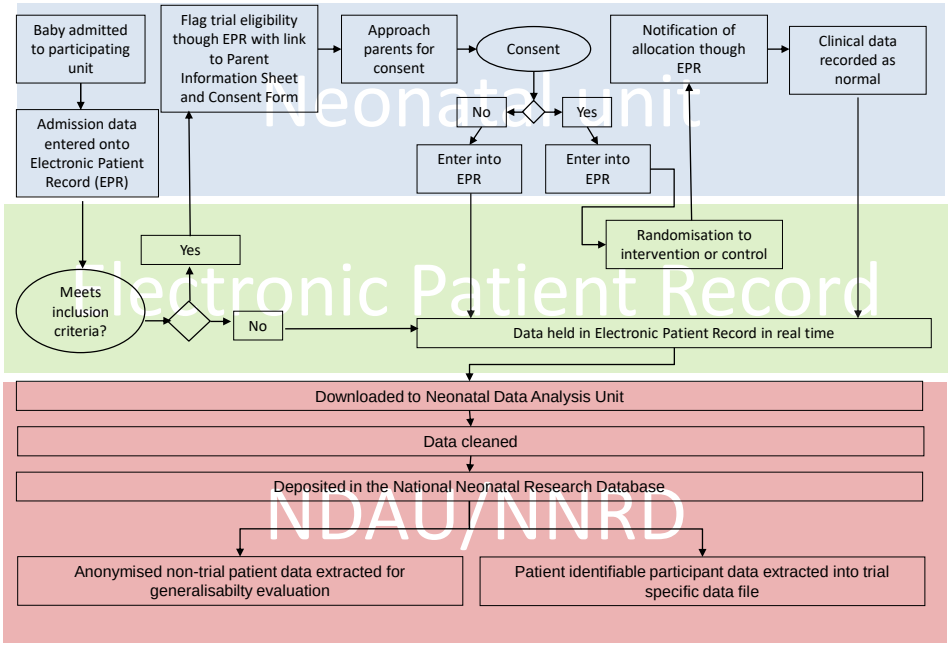
C: Compared to continued enteral feeding

O: Reduce the incidence of necrotising enterocolitis?



MRC Medical Research Council

- Power to detect a reduction in severe NEC (surgery and/or death) from 3.5% to 2.0% would require 2400 per group (90% power, α=0.05)
- ~9000 <32w gestation babies in UK annually



Schema courtesy of Dr Chris Gale

Separate responsibilities	Clinical teams, system supplier, data processor and controller
Point-of-care randomisation	System supplier
Consistent data capture	National data standard
Consistent case-definitions	Algorithm applied centrally; discrete data items recorded; no reliance on clinician-assigned diagnosis
Linkage	Specific regulatory approval to hold identifiers for explicit defined purposes
Contemporaneous data	Collaboration with NHS Digital
Funding model	Cost recovery through research supported

Buy-in

- Multiple types of use and outputs
- Multi-stakeholder steering board
- Newsletters
- Annual stakeholder conference
- Acknowledgement and authorship
- Clear data access process
- Parent involvement
- No data use without informing neonatal units (service evaluations) or explicit agreement (opt-out and opt-in approaches)
- Dissemination of protocols
- Publication of outputs
- Requirement by industry to commit to publish

Impact of managed clinical networks on NHS specialist neonatal services in England: population based study BMJ

OPEN ACCESS

C Gale *clinical research fellow*, S Santhakumaran *statistician*, S Nagarajan *data analyst*, Y Statnikov *data analyst*, N Modi *professor of neonatal medicine*, on behalf of the Neonatal Data Analysis Unit and the Medicines for Neonates Investigator Group

Survival of very preterm infants admitted to neonatal care in England 2008–2014: time trends and regional variation FN

Shalini Santhakumaran,[1,2] Yevgeniy Statnikov,[1,2] Daniel Gray,[1,3] Cheryl Battersby,[1,2] Deborah Ashby,[2] Neena Modi,[1,2] on behalf of the Medicines for Neonates Investigator Group

The effects of a one-to-one nurse-to-patient ratio on the mortality rate in neonatal intensive care: a retrospective, longitudinal, population-based study ADC Fetal & Neonatal edition

S I Watson,[1] W Arulampalam,[2] S Petrou,[1] N Marlow,[3] A S Morgan,[3] ES Draper,[4] N Modi,[5] On behalf of the Neonatal Data Analysis Unit (NDAU) and the Neonatal Economic, Staffing, and Clinical Outcomes Project (NESCOP) Group

(Ranked first of the top ten most read papers published in ADC FN in 2016)

Neonatal brain injuries in England: population-based incidence derived from routinely recorded clinical data held in the National Neonatal Research Database

Chris Gale,[1] Yevgeniy Statnikov,[2] Sena Jawad,[1] Sabita N Uthaya,[1] Neena Modi,[1] On behalf of the Brain Injuries expert working group

2018;103:F301-F306

ADC Fetal & Neonatal edition

Incidence and enteral feed antecedents of severe neonatal necrotising enterocolitis across neonatal networks in England, 2012–13: a whole-population surveillance study

Cheryl Battersby, Nick Longford, Sundhiya Mandalia, Kate Costeloe, Neena Modi, on behalf of the UK Neonatal Collaborative Necrotising Enterocolitis (UKNC-NEC) study group

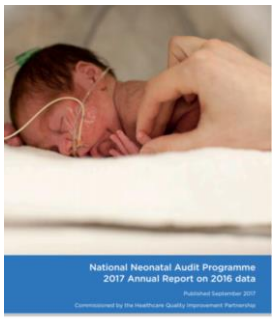
Summary

Background Necrotising enterocolitis is a neonatal gastrointestinal inflammatory disease with high mortality and severe morbidity. This disorder is growing in global relevance as birth rates and survival of babies with low gestational

Lancet Gastroenterol Hepatol 2016

The effects of designation and volume of neonatal care on mortality and morbidity outcomes of very preterm infants in England: retrospective population-based cohort study BMJ Open

S I Watson,[1] W Arulampalam,[2] S Petrou,[1] N Marlow,[3] A S Morgan,[3] E S Draper,[4] S Santhakumaran,[5] N Modi,[5] On behalf of the Neonatal Data Analysis Unit and the NESCOP Group



Association between early postnatal transfer and birth outside a tertiary hospital with mortality and severe brain injury: a whole-population study of extremely preterm infants BMJ

Helenius K, Longford N, Lehtonen L, Modi N, Gale C and the UK Neonatal Collaborative 2019 In press

Imperial College London

CARDIFF UNIVERSITY PRIFYSGOL CAERDYDD

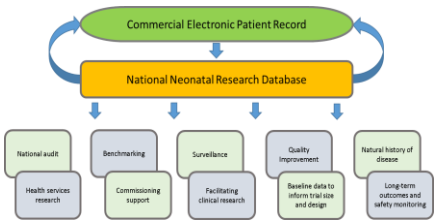
UNIVERSITY OF CAMBRIDGE

SPRING (Study of PReterm Infants and Neurodevelopment Genes)

Anita Thapur, Mick O'Donovan, Hilary Wong, Neena Modi

- To examine the feasibility of pragmatic recruitment and DNA sample collection in a neonatal intensive care setting
- To determine the acceptability to parents of prospective follow-up through routine data linkage and/or direct recall
- To test the hypothesis that the very preterm population is enriched for rare genetic deletions and duplications (copy number variants known to be implicated as neuropsychiatric risks

MRC Medical Research Council



- Recruited ahead of schedule
- All data obtained from the National Neonatal Research Database
- Of 883 infants recruited, 90.1% of parents agreed to future data linkage and 89.9% agreed to be recalled

Parent-patient contributions

Data quality assurance

BUDS
Better Use of Data to improve parent Satisfaction

Bliss
for babies born premature or sick

Dr Susanna Sakonidou

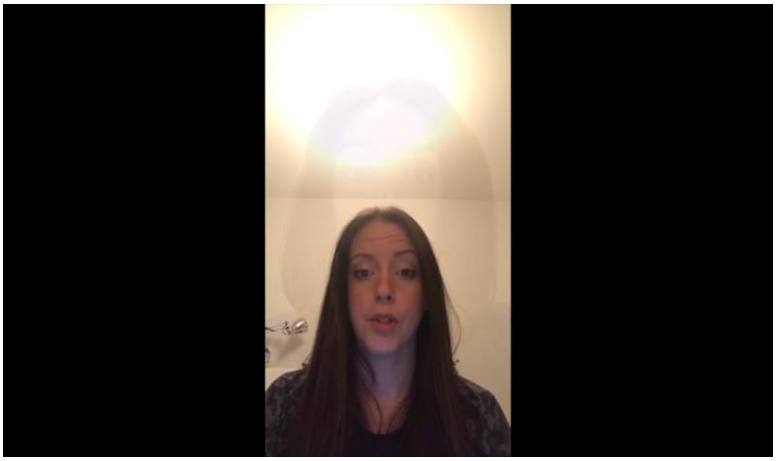
Core Outcomes Set for Neonatology

An international consensus process involving parents, clinicians, and researchers

- Survival
- Sepsis
- Necrotising enterocolitis
- Brain injury on imaging
- Retinopathy of prematurity (preterm only)
- Chronic lung disease (preterm only)
- Adverse events from intervention
- General gross motor ability
- General cognitive ability
- Visual impairment or blindness
- Hearing impairment or deafness
- Quality of life

Dr James Webbe

Parents and young people are our partners

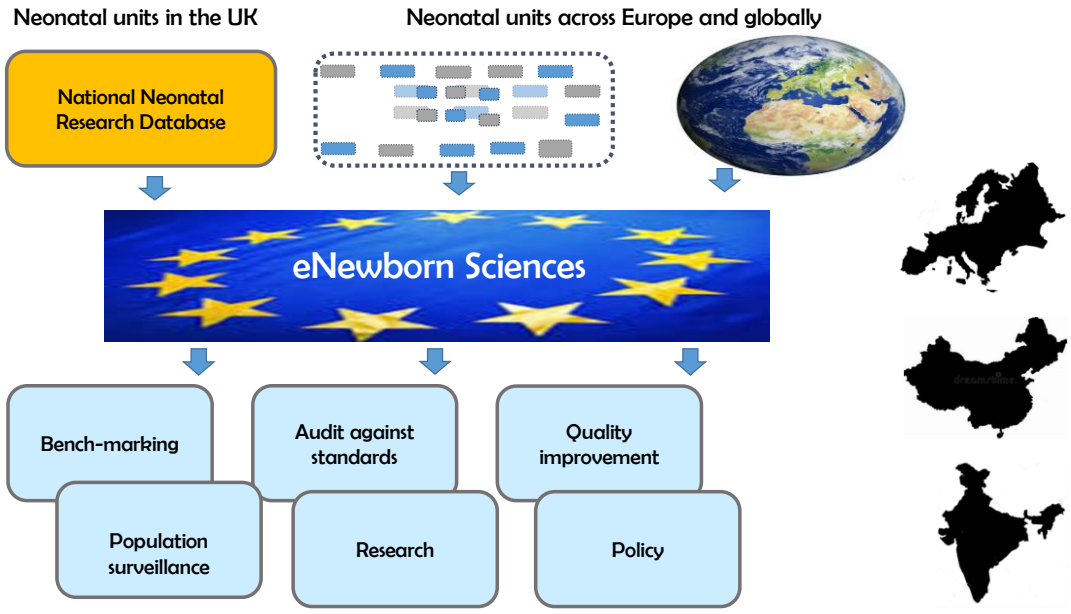


Parents and young people are part of our steering boards; they have been involved in focus groups, social media surveys, one-to-one interviews, Delphi consensus groups, and planning, designing, delivering and reporting studies

Video courtesy of Dr Susanna Sakonidou

Future directions

Our vision for global neonatology



The ALPHA Collaboration

ALPHA@ctc.usyd.edu.au

Advancing Large, simple, collectively Prioritised trials for neonatal Health outcomes Assessment worldwide

- There are complementary approaches to randomised trials to do meaningful clinical research
- We can integrate multiple approaches into routine clinical practice, including comparative effectiveness randomised trials
- Continuous evaluation of treatments must become synonymous with high quality and should be considered a standard of care

Communicate the rationale

- Insufficiently evidenced practice is a major risk to patient safety
- Involve and inform patients, parents, the public and policy-makers
- Explain the difference between comparative effectiveness and experimental medicine trials

Change mind-sets

- Put aside clinician bias
- Randomisation as an ethical approach

Address operational issues

- Ability to access contemporaneous data
- Data quality, completeness and timeliness
- Data standards

Imperial College London

Chelsea and Westminster Hospital NHS
NHS Foundation Trust

With thanks to the babies and their families, our collaborators and funders

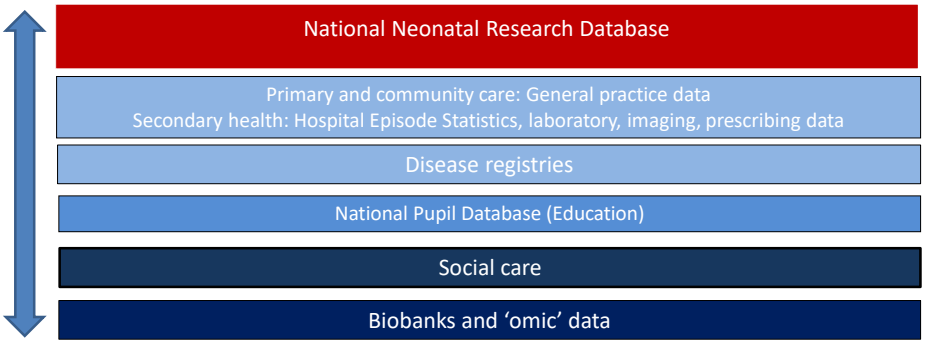
Linkage of the National Neonatal Research Database with primary care and other health data

Discover-NOW
the Health Data Research Hub for Real World Evidence in the UK

https://www.hdruk.ac.uk/infrastructure/the-hubs/

- One of seven pioneering UK data hubs opening October 2019
- Provides clinicians, researchers and scientists with access to de-identified linked patient information at scale in near to real time
- One of Europe's largest linked longitudinal data assets supported by consent to contact processes

Linkage of routine data sources to ascertain long term outcomes



Slide courtesy of Dr Cheryl Battersby