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Deliverable Leader:	Rolf F. Maier
Contributor:	Ulrika Aden (KI)

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EXECUTIVE SUMMARY

This document comprises recommendations and suggestions for quality assurance registers concerning people born very preterm (VPT; below 32 weeks of gestational age) or with a very low birth weight (VLBW; below 1,500 g). It represents a summary and essence of deliverables of several particular work packages within the RECAP preterm project.

VPT/VLBW cohorts are complex structures that need continued attention to timeliness, recruitment, attrition and quality of collected information in order to ensure high scientific standards and to allow appropriate translation into clinical practice or policy action.

Quality assurance registers are unique tools which can provide new scientific information and can deliver a comprehensive picture of consequences of VPT/VLBW birth over time. They are useful tools for clinicians, when making decisions in neonatal care of VPT/VLBW infants, for clinicians, when counseling parents with imminent VPT/VLBW birth or with VPT/VLBW infants, for researchers, when designing studies involving infants, children or adults born VPT/VLBW. They help to improve the care and outcome of individual VPT/VLBW individuals and the health care structures for VPT/VLBW infants.

RECAP Consortium Partners

Abbv	**Participant Organization Name**	**Country**
UMR	Philipps University Marburg	Germany
KI	Karolinska Institutet Stockholm	Sweden
EFCNI	European Foundation for the Care of Newborn Infants	Germany

OPEN ISSUES

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TABLE OF CONTENTS

Executive summary.....2
Open issues.....3
Table of contents.....4
1 Introduction.....5
  1.1 Purpose and Scope.....5
  1.2 References to other RECAP Documents.....5
  1.3 Definitions, Abbreviations and Acronyms.....6
2 Background.....7
3 Development And Target Groups of This document.....9
  3.1 Development.....9
  3.2 Target population.....9
  3.2 Target readers and users.....9
4 Specific Aspects of VPT/VLBW Cohorts.....10
  4.1 Inclusion criteria and sample size.....10
  4.2 Gender aspects.....10
  4.3 Environmental factors.....11
5 Ethical and legal aspects of VPT/VLBW registers.....12
6 Minimum data set For VPT/VLBW registers.....13
7 Recruitment for and retention in VPT/VLBW cohorts.....14
8 Infrastructure for cooperation in networks.....16
9 Statistical Analyses.....17
10 Follow-up.....18
11 Selection of Themes for future research.....19
12 Conclusion and outlook.....20
13 Literature references.....22

1 INTRODUCTION

1.1 Purpose and Scope

The RECAP preterm project's overall aim was to investigate and improve the health, development and quality of life of children and adults born very preterm (VPT; below 32 weeks of gestational age) or with a very low birth weight (VLBW; below 1,500 g) by establishing an ICT (information and communications technology) platform to integrate, harmonize and exploit the wealth of data from European and international cohorts of VPT/VLBW children and adults and their families constituted from the early 1980s to the present, together with data from national registers.

One particular aim was to develop recommendations for quality assurance registers for VPT/VLBW individuals based on the experience and the results from this project with respect to the organization and handling of large VPT/VLBW cohorts. For this purpose, the RECAP preterm project sought to develop standardized data on VPT/VLBW infants, children and adults that can be used for valid comparisons across studies, facilities and countries. The results form a basis for guidelines about the types of data to be included in quality assurance registers or audits in obstetric and pediatric hospitals.

This document intends to summarize and emphasize aspects to be considered when planning, conducting and analyzing such registers and when combining several cohorts and registers for meta-analyses based on the experiences of the RECAP preterm project.

1.2 References to other RECAP Documents

- RECAP Description of Work (Proposal)
- D2.2 Discussion manuscript re: 1) the ethics of research on data relating to vulnerable groups. 2) the consequences of the GDPR for reusing data of older cohorts
- D2.3 Recommendation manuscript on legal and ethical arrangements for data sharing
- D2.5 Article about Legal and Ethical tools for Data sharing
- D3.1 Meta-data catalogue with cross-cohort mapping
- D3.2 Report of cohort descriptions to aid future research
- D5.1 Report on a unifying missing data perspective to IPD problems
- D6.1 Report on available strategies for follow-up with strengths and limitations, including results of studies of children, parents and health care professionals

- D6.4 Report describing the performance of the designed tools and the results of the research projects
- D7.1. Report on priority research themes and approaches for a European platform
- D8.1 Common protocols for register studies
- D8.2 Data structure matrix for register data
- D9.2 Report of statistical analyses for identification of universal vs. culture specific outcomes; promotive and resiliency factors

1.3 Definitions, Abbreviations and Acronyms

Table 1 List of Abbreviations and Acronyms

Abbreviation/ Acronym	DEFINITION
CP	Cerebral palsy
FAIR	Findable, Accessible, Interoperable, Reusable
GDPR	General Data Protection Regulation
ICT	Information and communications technology
NICU	Neonatal intensive care unit
VLBW	Very low birth weight
VPT	Very preterm
WP	Work package

2 BACKGROUND

Every year approximately 50,000 infants are born very preterm (VPT; below 32 weeks of gestational age) or with a very low birth weight (VLBW; below 1,500 g) in Europe. VPT/VLBW births constitute fewer than 2 % of all births across Europe, but they account for up to half of perinatal and infant deaths, children with impairments and disabilities and more than a third of the health and educational budgets for children [45]. While survival of these children has increased markedly over the last decades, they are at higher risk of visual and auditory deficits, poor respiratory outcomes, cerebral palsy (CP), impaired motor and cognitive ability and psychiatric disorders than children born at term [12, 15, 17, 20, 24, 30, 42, 51]. Up to a third of these children and their parents face a life course with significant morbidity, dependency and socioeconomic challenges [21]. They have an increased risk for poor academic attainment and special educational needs compared with their term-born peers [8, 18, 22, 26]. VPT/VLBW children and adolescents have also been found to have more emotional disorders such as anxiety, depression, social withdrawal and difficulties making friends [21, 31]. They are more likely to become the target of social exclusion such as being bullied with long term consequences on mental health [50]. Apart from physical health, studies suggest that mental health, quality of life, partnering, family life and employment chances and wealth may be adversely affected in adults born VPT/VLBW [4, 6, 14, 28, 36, 39, 48].

Obstetric and neonatal care as well as the knowledge about underlying causes of VPT/VLBW birth have evolved over the past decades. As a consequence, survival at the lower end of gestation has increased, but it is still unclear whether developmental outcome has similarly improved [2, 46, 53].

Evidence-based information about prognosis and future complications are needed to assess the effectiveness of medical care and social programs, make the best decisions for these children and intervene early to prevent or mitigate health and developmental problems.

Studies which have compared mortality across countries and neonatal units using comparable indicators have revealed large survival differences among VPT/VLBW births after adjusting for differences in patient characteristics [11, 29, 52]. The existence of disparities in risk-adjusted mortality suggests that substantial gains in survival are possible using current medical knowledge [1, 11, 16, 40, 54]. Studies showing variations across national cohorts in survival and neonatal outcomes suggest that evidence-based perinatal care is not optimally applied in

Europe and raise the possibility that substantial gains could be achieved if known best practices were more broadly applied [54]. Comparisons of practices for the care of VPT/VLBW infants across countries and units supports this assertion, as practices are not always consistent with the best scientific evidence, including non-use of treatments shown to be effective and safe and use of others for which evidence is limited or where safety is of concern [7, 8, 13, 41, 43, 47, 54]. Comparative descriptive data on outcomes and health care are a key tool underpinning evidence-based policy and research.

It is unclear which outcomes of VPT/VLBW infants are universal and which vary according to either obstetrical or neonatal management, the available social or educational support or the cultural context. Identifying modifiable factors is key to effective policy development and intervention.

Quality assurance registers can build unique sources of information on the incidence and risk factors of VPT/VLBW birth, efficacy and safety of particular treatment options, short-term and long-term outcome of VPT/VLBW children and adults, the burden of VPT/VLBW birth for the child, the family, the health care system and the society and offers the chance for epidemiologic and clinical changes ahead.

3 DEVELOPMENT AND TARGET GROUPS OF THIS DOCUMENT

3.1 Development

This document results from the RECAP preterm project and represents a summary and essence of deliverables of several particular work packages (WPs) within this project.

3.2 Target population

This document refers to people born very preterm (VPT) or with very low birth weight (VLBW) independently of their actual age, thus including concerned infants, children and adults, and to their families.

3.2 Target readers and users

This document is directed to a broad range of stakeholders from multiple disciplines dealing with and related to people born VPT/VLBW. This includes in particular the research community, clinicians and health care providers, physicians, psychologists, social workers, educators, patients, individuals born VPT/VLBW, parents of VPT/VLBW infants and their organizations, public health decision-makers, economists, health insurance companies, policy makers and the interested general public.

4 SPECIFIC ASPECTS OF VPT/VLBW COHORTS

4.1 Inclusion criteria and sample size

VPT/VLBW cohorts are distinct from general population birth registers in that they cover all VPT/VLBW infants and provide detailed documentation on the obstetrical and neonatal medical characteristics, complications and treatments that are needed for research on this population. These data items require precise protocols for measurement in order to provide valid and comparable results, and are therefore often not realistic in general birth cohorts where they are not relevant for 98 % of included infants.

VPT/VLBW cohorts follow a population-based design – as opposed to networks of selected specialized units – in order to increase validity and ensure representativeness. As VPT/VLBW infants represent a heterogeneous group and are only about 2 % of the overall population of births, it is particularly challenging to achieve adequate sample sizes to obtain robust results in this particular population. Getting an adequate sample size needs a large geographic spread and a long inclusion period.

VPT/VLBW birth has multiple causes and many consequences that are potentially mediated by its etiology, medical care provided to the mother or child, pediatric, social and educational support and the social and economic environment. The low prevalence of some outcomes after VPT/VLBW birth require large samples to allow for accurate risk estimates and inference. Unfortunately, individual cohorts do not usually have sufficient sample sizes for in-depth analyses of many key sub-groups which represent only a small fraction of all births. Further, each cohort is anchored in its time and place and the generalizability of findings to other settings and other age groups cannot be addressed.

Combining several cohorts and registers is a promising instrument to solve the problem of inadequate sample sizes (see below).

4.2 Gender aspects

VPT/VLBW cohorts and registers must address key issues related to gender because developmental differences between girls and boys may create gender-specific intervention effects due to biological as well as socio-cultural factors. The experiences of parents may also differ by gender and therefore both mothers and fathers should be considered.

Some different outcomes between girls and boys may reflect more general differences in the development of girls and boys which affect the impact of specific impairments, such as brain lesions or respiratory morbidity on later health, development and behavior. However, it may also reflect differences in vulnerability to the sequels of VPT/VLBW birth by gender [33, 37, 44]. Statistical models should adjust for the gender of the child and interaction terms with key exposures should be assessed.

Gender is also an important consideration in the assessment of family experiences, as mothers and fathers have been shown to react differently both to the event of VPT/VLBW birth and admission to NICU, and to the care of a child with chronic disease [3, 19, 38].

4.3 Environmental factors

Most VPT/VLBW cohort studies have so far focused on assessing medical and biological factors associated with VPT/VLBW birth. Overall, it was found that VPT/VLBW studies, with very few exceptions, have in the past failed to assess a sufficient range of environmental factors that are modifiable and would be relevant for targeting of early prevention and intervention programs. The inclusion of sociodemographic data and environmental factors in future assessments will be fundamental in unravelling what factors across life may change the developmental trajectories of individuals born VPT/VLBW and inform interventions and health policies. Identification of protective and resilience factors across adult VPT/VLBW cohorts are needed. Registers with large sample sizes give excellent opportunities for conducting extensive adjustments for potential confounders in the analyses. As longitudinal data are always at risk, that bias is introduced due to temporal trend(s), factors associated with time should always be considered.

5 ETHICAL AND LEGAL ASPECTS OF VPT/VLBW REGISTERS

Establishing and continuing cohorts or registers of VPT/VLBW infants includes a complex set of ethical and legal aspects to be considered. This applies even more when a merge of several cohorts or registers from different countries is intended. Most of all ethical and legal aspects are connected with privacy and data protection. General and specific rules have to be followed and national and international regulations to be respected [32, 34].

Sampling, storing and analyzing data of cohorts or registers must be compliant with the Helsinki Declaration of Ethical Principles in Medical Research and must be approved by national authorities or local Medical-Ethical Committees in the country of origin of each cohort.

The most important ethical issue is that the cohort or register participants were or may still be a vulnerable group. They still are or were minors at the time of data collection with informed consent provided by the parents.

Researchers within registers must agree on and organize privacy, ethical, legal and scientific aspects, data sharing and data access, taking into account requirements with respect to reuse and access of available data, with a particular focus on vulnerable people.

During long follow-up periods rules and insights may change with large country-specific variations with respect to data protection.

Within the RECAP preterm project, rules were established for a sustainable European governance model to share and integrate data from a large number of different cohorts on children and adults born VPT/VLBW and to perform research on the combined data, in line with the ethical and legal requirements and the EU General Data Protection Regulation (GDPR) with respect to data sharing and big data analyses and in line with the FAIR (Findable, Accessible, Interoperable, Reusable) principles of data management. The governance model includes specific legal arrangements for data access, authorization and data transfer agreements, the conditions for the secure handling of those data and arrangements for individual feed-back on results of research.

6 MINIMUM DATA SET FOR VPT/VLBW REGISTERS

Many of the studies reporting neonatal mortality and morbidity as well as long term outcome of infants born VPT/VLBW are almost impossible to compare because of the multiple definitions used and the heterogenous items obtained. For sharing of individual patient data from VPT/VLBW birth cohorts and registers, mapping and harmonization of the data items available in these cohorts is necessary, on both already collected and newly acquired data.

To ensure that consistent terms are used across future studies, the RECAP preterm consortium suggests a universal list of terminologies and definitions. To facilitate pooling of individual patient data from VPT/VLBW birth cohorts and registers, to increase statistical power and enhance international comparison a framework was provided for standardizing existing data and informing on-going and future data collection. This framework helps to develop comparable indicators for benchmarking survival, morbidity and long-term outcome in VPT/VLBW cohorts and registers.

A list of data items that is the minimum that should be measured and reported in all VPT/VLBW birth cohorts and registers was developed within the RECAP preterm project using a consultation methodology: Using several steps of a Delphi consensus process with experts including researchers, clinicians, people concerned and parents, a subset of variables for measurement and classification of exposures and outcomes that most frequently occur in participating VPT/VLBW cohort studies was identified. The resulting minimum data set on VPT/VLBW infants, children and adults will facilitate future collaborative work by ensuring variables are comparable across different studies, facilities and countries and can be used for valid benchmarking in quality assurance registers.

7 RECRUITMENT FOR AND RETENTION IN VPT/VLBW COHORTS

The recruitment of VPT/VLBW cohorts and registers require participation of all maternity and neonatal units within a defined area, the commitment of health personnel and parents.

One of the major problems for VPT/VLBW cohorts is the declining participation willingness, while at the same more data are available routinely in administrative databases and new methods for maintaining contact with participants and collecting data are becoming available. The steadily declining participation rate in epidemiologic studies over the past few decades has raised concerns regarding representativeness and study validity.

Also, retention of participants in cohort studies and registers, especially during long follow-up periods, is a major challenge and a critical limiting factor. During the last few decades, also retention rates in VPT/VLBW cohorts have declined following the observed general trend in population studies.

VPT/VLBW birth is associated with social and economic risk factors such as low parental educational status, poverty, migrant status and social isolation, which are also often negatively associated with child health and development. These factors are also associated with selective dropout of VPT/VLBW cohorts [49].

Within the RECAP preterm project, the perspectives of parents, healthcare professionals and researchers on participant retention in longitudinal cohorts across diverse socio-geographic and cultural settings were collected and motivations, deterrents and facilitators for participation and retention in long-term studies were identified [27].

Decreasing study enrolment rates and higher rates of loss to follow up of enrollees (manifested by missed appointments, unavailability to complete specific questionnaires, and missing scheduled interval exams) are indicative of study fatigue and a decreased commitment to longitudinal investigations among populations and participants. Additionally, traditional recruitment and engagement approaches such as face-to-face assessments are costly, have complex logistics and have demonstrated only limited success in improving study participation.

New approaches are therefore needed to augment participation in longitudinal cohort studies and to assure the quality of information collected. Current generations of children born VPT/VLBW are growing up using smart phones and about 95 % of the European population has internet access. New strategies to recruit and to bond the participants to cohort studies and registers include smart phones (e.g., calls, voicemail, texting), social media, and dedicated websites. The leveraging of web-based interventions must necessarily be participant-centered: utilizing a gamification approach and involving the active participation of target populations in setting the scientific and research agenda. However, electronic methods are just one tool in the tool set needed to get high participation. As those with disabilities may have more problems in access to electronic media and problems with completing, face to face visits will need to remain to reduce bias towards the “well off”. In this context, particular attention must be given to ensuring that electronic tools are data protection compliant.

8 INFRASTRUCTURE FOR COOPERATION IN NETWORKS

Research on VPT/VLBW survival and long-term outcomes necessarily needs large sample sizes and longitudinal designs. New cohorts have to be reconstituted over time and results need to be compared across cohorts.

Within the RECAP preterm project, an ICT (information and communications technology) platform was established, which represents a sustainable, geographically diverse and multidisciplinary database of national and European cohorts and registers of children and adults born VPT/VLBW.

The RECAP preterm platform makes it possible to increase the power and generalizability of research on VPT/VLBW individuals. The broad temporal, geographic, cultural and health system diversity makes it possible to study the impact of socioeconomic and organizational contexts and determines the generalizability of outcomes for VPT/VLBW populations.

The large sample sizes achieved by pooling data allows for stratified sub-group analyses of sociodemographic and clinical characteristics, neonatal complications and less prevalent medical conditions which currently cannot studied even in large national cohorts.

These analyses are needed for a better understanding of the origins of VPT/VLBW health and developmental outcomes and for more effective, evidence-based, personalized interventions and prevention. Given their historical richness, combining data across cohorts also makes it possible to evaluate changes in outcomes over time, providing important information on how the evolution in care and survival of these high-risk babies has changed their developmental outcomes and quality of life.

9 STATISTICAL ANALYSES

Lacking adherence to appointments and increasing attrition of participants in longitudinal studies over time provoke missing values lowering the validity of cohort studies and registers.

A specific work package (WP) within the RECAP preterm project describes a unifying missing data perspective to problems related to combining individual patient data for cohorts that track VPT/VLBW children. Multiple imputation represents a generic solution. When properly executed, this approach results in appropriate statistical estimates and may be especially beneficial to solve data combination problems for which no proper solution yet exists, or for augmenting existing procedure for which there is no good quantification of the uncertainty caused by data combination.

10 FOLLOW-UP

Many studies in VPT/VLBW infants stopped data acquisition at the time of discharge from the neonatal unit. With this approach, the results are restricted to mortality and morbidity during the neonatal period. However, the aim of neonatal care is a long-term outcome similar to that of infants born at term and a normal quality of life.

As the consequences of VPT/VLBW birth are highly heterogeneous and can only be fully assessed in childhood, adolescence or even adulthood, the evaluation requires long-term follow-up until adulthood. The real extent of impairment and impact on quality of life, as well as the child’s compensatory mechanisms and potential, clarifies only with time. At first discharge home from neonatal hospitalization the long-term prognosis for each individual child is in most cases unknown and it is not possible to identify with certainty children who will develop specific impairments, how long they will last nor determine their severity.

While the likelihood of developing specific neurological impairments is associated with biological risk factors and the clinical course during hospitalization, many infants with well-known risk factors will never develop an impairment, while others without known risk factors may experience poor long-term neurodevelopmental outcomes. Social and environmental factors need to be taken into account in predicting long-term outcome. Timeliness of identification of health problems, and quality of care provided, may also modulate outcomes.

Follow-up, however, consumes significant resources because of the multidisciplinary specialized staff needed for clinical and developmental assessments and interventions, and the logistics and coordination required to maintain contact with children after discharge. Therefore, implementation of follow-up programs must be evaluated with regard to their cost-effectiveness [35]. Nevertheless, routine follow-up should be implemented at least at 2 years of corrected age and at transition to school as a minimum. This is also to provide quality assurance of the neonatal care.

11 SELECTION OF THEMES FOR FUTURE RESEARCH

Quality assurance registers represent a valuable source for future research. Themes for research on health and care of VPT/VLBW children and adults should be developed based on the input from researchers, clinicians, educators, policy makers, persons concerned and their families [55]. Biological, clinical, and socioeconomic determinants of disease and health outcomes associated with VPT/VLBW birth should be identified in order to facilitate risk and resiliency assessments, thus allowing for the development of evidence-based, stratified, and personalized guidelines and policies for health maintenance, screening, early diagnosis, and intervention.

Future research should include short-term and long-term effects of interventions currently applied for VPT/VLBW infants such as medication, ventilation and nutrition and their interaction with genetics, clinical factors and the social and educational environment in order to identify and develop individualized diagnostic, preventive and therapeutic interventions.

Specific subgroups should be identified to make preventive and curative treatments more effective and efficient. It should also be identified what are the universal protective factors and resilience mechanisms that optimally enhance the life chances of VPT/VLBW infants and influence health, social and economic outcomes of adults born VPT/VLBW [25].

Future research should also carry out research on the families of VPT/VLBW children. Parents are faced with multiples stressors during their infant's hospitalization and often have to master the challenge of dealing with multiple births. Stress can lead to increased risk of postnatal mental illness such as depression, leading to poorer caretaking [23]. However, there is also remarkable evidence for the resilience of parents showing that mothers of VPT/VLBW infants are as sensitive in their interaction with their offspring as mothers of term born infants despite their stress experience [5].

The level of information, care and support received by families of VPT/VLBW infants still differs widely across Europe. The involvement of user organizations and families is another important component of future study planning.

A structured consensus process with stakeholders, including researchers, health care professionals, people concerned, families and user organizations, should be made at all levels of planning and implementation of studies, making the path from ideas to application a comprehensive one.

12 CONCLUSION AND OUTLOOK

VPT/VLBW cohorts are complex research structures that need continued attention to timeliness, recruitment, attrition and quality of collected information in order to ensure high scientific standards and to allow appropriate translation into clinical practice or policy action.

The RECAP preterm project sought to develop standardized data on VPT/VLBW infants, children and adults that can be used for valid comparisons across studies, facilities and countries. These results form a basis for guidelines about the types of data that should be included in quality assurance registers or audits in obstetric and pediatric hospitals.

Like in other patient groups [10], quality assurance registers are unique tools which can provide new scientific information and can deliver a comprehensive picture of consequences of VPT/VLBW birth over time. They are useful tools for clinicians, when making decisions in neonatal care of VPT/VLBW infants, for clinicians, when counseling parents with imminent VPT/VLBW birth or with VPT/VLBW infants, for researchers, when designing studies involving infants, children or adults born VPT/VLBW. They help to improve the care and outcome of VPT/VLBW individuals and the health care structures for VPT/VLBW infants.

The following table comprises what can be learned from the RECAP preterm project for cohort studies and quality assurance registers in people born very preterm (VPT) or with very low birthweight (VLBW).

Topic	**Recommendation**	**Rationale**
Inclusion	Population based over a long time	Validity and representativeness
Sample size	• Adequate numbers over a long period • Combination of several cohorts	• Small and heterogenous population • Low prevalence of some outcomes
Duration	From birth until adulthood	Consideration of long-term consequences
Recruitment and retention	Diverse set of tools including electronic tools	High attrition rate over time
Follow up	At least at 2 years corrected age and at school entry	For quality assurance in neonatology
Confounders	• Consideration of gender • Consideration of social and other environmental factors	• Differences in some outcomes between girls and boys • Large influence of environment across life span
Legal and ethical aspects	Compliance with international, national and local regulations	Privacy protection of participants
Infrastructure	Cooperation in networks	Increased sample size by pooling

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