BMJ Open

Supplemental oxygen strategies in infants with bronchopulmonary dysplasia after the neonatal intensive care unit period: study protocol for a randomised controlled trial (SOS BPD study)

Stephanie Balink,1 Wes Onland,2,3 Elianne J L E Vrijlandt,4 Eleni-Rosalina Andrinopoulou,5 Arend F Bos,6 Peter H Dijk,6 Lucas Goossens,7 Anthon R Huismann,8 Debbie H Nuytemans,2,3 Irwin K M Reiss,9 Arwen J Sprij,10 André A Kroon,9 Anton H van Kaam,2,3 Marielle Pijnenburg,1 on behalf of the SOS BPD study group

ABSTRACT

Introduction Supplemental oxygen is the most important treatment for preterm born infants with established bronchopulmonary dysplasia (BPD). However, it is unknown what oxygen saturation levels are optimal to improve outcomes in infants with established BPD from 36 weeks postmenstrual age (PMA) onwards. The aim of this study is to compare the use of a higher oxygen saturation limit (≥95%) to a lower oxygen saturation limit (≥90%) after 36 weeks PMA in infants diagnosed with moderate or severe BPD.

Methods and analysis This non-blinded, multicentre, randomised controlled trial will recruit 198 preterm born infants with moderate or severe BPD between 36 and 38 weeks PMA. Infants will be randomised to either a lower oxygen saturation limit of 95% or to a lower limit of 90%; supplemental oxygen and/or respiratory support will be weaned based on the assigned lower oxygen saturation limit. Adherence to the oxygen saturation limit will be assessed by extracting oxygen saturation profiles from pulse oximeters regularly, until respiratory support is stopped. The primary outcome is the weight SD score at 6 months of corrected age. Secondary outcomes include anthropometrics collected at 6 and 12 months of corrected age, rehospitalisations, respiratory complaints, infant stress, parental quality of life and cost-effectiveness.

Ethics and dissemination Ethical approval for the trial was obtained from the Medical Ethics Review Committee of the Erasmus University Medical Centre, Rotterdam, the Netherlands (MEC-2018–1515). Local approval for conducting the trial in the participating hospitals has been or will be obtained from the local institutional review boards. Informed consent will be obtained from the parents or legal guardians of all study participants. Trial registration number NL7149/NTR7347.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first randomised controlled trial that aims to identify the optimal lower limit of oxygen saturation for infants with moderate or severe bronchopulmonary dysplasia to improve growth and respiratory health.

⇒ Adherence to the assigned limit for weaning supplemental oxygen will be increased by collecting oxygen saturation profiles twice (in hospital) or once (at home) weekly.

⇒ Limitations of this study are that the study is not blinded and that protocols among the participating centres to wean oxygen or respiratory support are not standardised.

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is the most common complication of extreme preterm birth. The pathogenesis of BPD is complex and multifactorial: prenatal and postnatal risk factors such as intrauterine growth restriction, pregnancy-related hypertensive disorders, mechanical ventilation and infections all may impact on the immature, developing lungs of extremely preterm infants.1 As a consequence, there is an arrest in lung development characterised by a decreased number of alveoli, which are larger and simplified, combined with small airway injury and abnormal development of the pulmonary vasculature.2 Despite advances in perinatal and neonatal care, the incidence of BPD remains high, affecting almost half of...
infants born <28 weeks of gestation who survived to 36 weeks postmenstrual age (PMA).13

Infants with BPD may experience poor respiratory health and impaired lung function throughout childhood, even persisting into adulthood.13 Particularly the first years of life are characterised by prolonged use of supplemental oxygen, frequent respiratory symptoms and an increased risk of hospitalisation.6,7 Having a child with BPD also poses an important burden on family life and is associated with a decreased quality of life of caregivers.8

Supplemental oxygen is the most important treatment for preterm infants with established BPD. It reduces respiratory symptoms, reduces or prevents pulmonary hypertension and has possible beneficial effects on growth and neurodevelopment.9 However, no study has ever examined the optimal oxygen saturation (SpO2) target in children with established BPD, while both too little and too much oxygen may lead to serious adverse events (SAE).10 Few guidelines include recommendations for SpO2 levels in infants with BPD. The European Respiratory Society guideline on long-term management of children with BPD suggests the use of a lower limit of SpO2 of 90% when using supplemental oxygen.11 The American Thoracic Society Guideline on home oxygen therapy suggests a level of 93% as minimum threshold.12 However, the level of evidence supporting these recommendations is low. This has led to substantial practice variation in the applied SpO2 limits in infants with BPD still receiving respiratory support and/or supplemental oxygen after 36 weeks PMA.

In contrast to the limited evidence available after 36 weeks of PMA, optimal SpO2 targets have been extensively studied in preterm infants before the age of 36 weeks of PMA. The Supplemental Therapeutic Oxygen for Prethreshold Retinopathy Of Prematurity (STOP-ROP) trial, the Benefits Of Oxygen Saturation Targeting (BOOST) trial and the Neonatal Oxygen Prospective Meta-analysis (NeOProM) Collaboration (including five randomised controlled trials) all compared different SpO2 targets in preterm infants before 36 weeks of PMA.13–15 All trials studied slightly different SpO2 target ranges (table 1).

The STOP-ROP trial found no differences in progression of ROP, but targeting a higher SpO2 did lead to a higher incidence of respiratory morbidity (pneumonia or exacerbations of chronic lung disease).15 However, this study was not designed, nor powered for respiratory outcomes. The BOOST trial found no differences between the two groups on growth or neurodevelopment at 12 months corrected age, but infants in the higher SpO2 range had an increased length of oxygen therapy and required home oxygen more often.14 The meta-analysis of the NeOProM Collaboration showed that targeting a higher SpO2 range decreased the incidence of death and necrotising enterocolitis, but the incidence of ROP requiring treatment was higher in the higher saturation group. The use of supplemental oxygen at 36 weeks PMA was higher in the group with a higher SpO2 target range, due to the study protocol.16 The incidence of blindness, severe hearing loss and cerebral palsy was similar across the groups.15

Based on the outcomes of these studies, the American Academy of Pediatrics concluded that the optimal SpO2 range for extremely low birth weight infants remains unknown, but that an SpO2 range of 90%–95% may be safer than 85%–89%.17

It is important to acknowledge that there are several reasons why the results of these oxygen targeting studies before 36 weeks PMA may not be extrapolated to infants with established BPD who have reached near term age. First, the lungs have reached a new stage of development as alveolar growth starts from approximately 36 weeks of gestation.18 In addition, there is a transition from lung development to lung growth in infancy and childhood, as lung volume will increase about 23 times between birth and adulthood in healthy subjects.18 Second, it has been suggested that vulnerability to oxidative stress is less pronounced at 36 weeks PMA compared with the first weeks of life as antioxidant systems have matured. Third, also the pulmonary vascular system undergoes important differentiation during the different stages of lung development.19 The optimal SpO2 range to prevent pulmonary vascular disease may be different from the range to improve pulmonary vascular disease. Therefore, infants with established BPD after 36 weeks of PMA may require another approach to oxygen treatment than infants with developing BPD before 36 weeks PMA.

In summary, there is a lack of evidence on the optimal SpO2 levels in infants with established BPD from 36 weeks PMA onwards to optimise respiratory health. Therefore, the aim of this study is to compare a higher SpO2 (ie, 95% lower limit) to a lower SpO2 (ie, 90% lower limit) in infants with moderate or severe BPD from 36 weeks PMA and onwards. Our hypothesis is that a higher SpO2 target in infants with established moderate or severe BPD, improves weight gain and lung growth.

### Table 1

<table>
<thead>
<tr>
<th>Trial</th>
<th>Lower SpO2 range</th>
<th>Higher SpO2 range</th>
</tr>
</thead>
<tbody>
<tr>
<td>STOP-ROP trial</td>
<td>89%–94%</td>
<td>96%–99%</td>
</tr>
<tr>
<td>BOOST trial</td>
<td>91%–94%</td>
<td>95%–98%</td>
</tr>
<tr>
<td>NeOProM Collaboration</td>
<td>85%–89%</td>
<td>91%–95%</td>
</tr>
</tbody>
</table>

SpO2, oxygen saturation.

### OBJECTIVES

The primary objective is to investigate whether a higher SpO2 (ie, 95% lower limit) leads to a higher weight at 6 months corrected age, as a surrogate for lung growth. Secondary objectives are to determine if a higher SpO2 translates into higher weight and height at 12 months corrected age, less healthcare consumption, less infant...
stress, better quality of life for parents or caregivers and more favourable cost-effectiveness.

METHODS AND ANALYSIS

Study design and setting

The SOS BPD study is an open, randomised controlled trial and will be conducted in the Netherlands in approximately (but not limited to) 30 hospitals. In the Netherlands, the care for extremely preterm born infants is concentrated in nine hospital clusters. Each cluster consists of one or two level 3 Neonatal intensive care units (NICU) and several post-intensive care/high care (post-IC/HC) units in surrounding level 2 centres. The participating hospitals include 10 NICU centres and 20 post-IC/HC units. A list of recruiting sites is provided in online supplemental file 1. The SOS BPD study is conducted within the Neonatology Network Netherlands (N3) organisation.20

The protocol for this trial is reported based on the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Checklist21 (online supplemental file 2: SPIRIT Checklist).

Study population

Infants with moderate or severe BPD, born before 32 weeks of gestation, who still receive respiratory support at 36 weeks PMA are eligible for inclusion. BPD is defined as the use of supplemental oxygen (ie, >21% oxygen) for ≥28 days since birth.22 Depending on the level of respiratory support at 36 weeks PMA, BPD severity is classified as mild, moderate or severe (table 2). An oxygen reduction test will be used to assess severity if indicated.23

Written informed consent will be obtained from parents or legal guardians by the local PI of the hospital where the participant is admitted between 36 and 38 weeks PMA, BPD severity is classified at 36 weeks PMA.22 The inclusion criteria are significant congenital heart disease (not being patent ductus arteriosus, small atrial septal defect, ventricular septal defect), pulmonary hypertension with evidence of pulmonary hypertension.9 Also, with a lower limit of 95%, there is a clear contrast between the two groups. A lower limit of 90% was chosen for the second group, since this lower limit is advised in the BPD guideline of the European Respiratory Society and SpO2 values <90% have been associated with adverse outcomes.11 17

During hospitalisation, respiratory support and oxygen supplementation will be adjusted based on the assigned lower limit of SpO2, as part of daily clinical care. Two times a week, SpO2 data will be logged from pulse oximeters and stored on a USB stick. Logging frequency differs from hospital to hospital where the participant is included. This is a non-blinded study, since it is not feasible to blind treating physicians and parents for SpO2 values as measured with pulse oximetry in the hospital or at home.

Randomisation

Between 36 and 38 weeks PMA, participants will be randomised 1:1 to one of two parallel treatment arms: weaning of supplemental oxygen and respiratory support based on an SpO2 lower limit of 95% or weaning based on a lower limit of 90%.

For the randomisation procedure, an electronic data capture system that uses a computer-generated randomisation list (Castor EDC) will be used.24 We will block randomisation, with a variable block size (4–8). Allocation will be stratified by NICU centre (10 centres) and BPD severity (moderate or severe). In case of multiple birth, the firstborn infant will be randomised according to standard procedures. Siblings will be manually assigned to the same treatment arm as the firstborn infant.

Enrolment, registration and electronic randomisation in Castor EDC will be carried out by the local PI of the hospital where the participant is included.

This is a non-blinded study, since it is not feasible to blind treating physicians and parents for SpO2 values as measured with pulse oximetry in the hospital or at home.

Study procedures

After randomisation, participants are assigned to one of the two treatment arms. A lower limit of 95% was chosen for the first group, as the median SpO2 in preterm infants without BPD is ≥95%25 and SpO2 ≥94% reduces the incidence of pulmonary hypertension.9

Severity classification

<table>
<thead>
<tr>
<th>Definition of BPD</th>
<th>Severity classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment with supplemental oxygen for ≥28 days</td>
<td>Breathing room air or nasal cannula with ≤1 L flow, FiO2 21%</td>
</tr>
</tbody>
</table>

Severity is classified at 36 weeks PMA.22

BPD, bronchopulmonary dysplasia; FI O2, fraction of inspired oxygen; HFNC, high flow nasal cannula; PMA, postmenstrual age.
SpO₂ data and group assignment, the medical team will receive advice to actively wean or increase supplemental oxygen. In case participants are discharged on home oxygen, SpO₂ data will be logged from a pulse oximeter at home by the parents once weekly and will be sent to the research team through encrypted file transfer. Feedback and advice to adjust supplemental oxygen will be given to the parents and treating physician.

SpO₂ profiles will be obtained until 1 week after discontinuation of respiratory support. If an infant is readmitted to hospital while still on supplemental oxygen, the assigned SpO₂ lower limit will be kept. If infants are readmitted after they were weaned from supplemental oxygen for at least 2 weeks, the lower SpO₂ limit will be set according to the local hospital policy.

In order to follow routine clinical care as much as possible, physicians will wean supplemental oxygen according to their local hospital protocol. If no such protocol is available, a study specific standard operating procedure will give recommendations on weaning supplemental oxygen (online supplemental file 4).

In order to improve feasibility and generalisability, the use of diuretics, inhaled or oral corticosteroids, other medications, fluid restriction and feedings will be according to national guidelines or local policies. Data on these parameters will be collected during the study.

Interpretation of SpO₂ profiles
If the time spent below the assigned lower limit of SpO₂ is ≥10% of the recorded time (equivalent to <90% of the time spent above the lower limit), the treating team is advised to increase supplemental oxygen and/or respiratory support. When the SpO₂ is below the assigned lower limit for ≤10% of the time (equivalent to >90% of the time spent above the lower limit), the treating team is advised to wean supplemental oxygen and/or respiratory support.

The British Thoracic Society Guideline for home oxygen in children suggests that the lower limit target SpO₂ should be met for at least 95% of a stable recording period. However, this does not take into account that a SpO₂ should be met for at least 95% of a stable recording period. This does not take into account that a SpO₂ should be met for at least 95% of a stable recording period.

Outcomes
The primary outcome of the study is weight SD score (SDS) at 6 months corrected age as a surrogate for lung growth. Increased weight and weight gain during infancy are associated with better lung function and structure. Appropriate growth is also an important measure of general well-being in infancy, while growth delay is associated with an increased risk of future respiratory and cardiovascular disease and impaired intellectual outcomes. Growth failure is very common in infants with BPD. The exact underlying mechanisms are unknown, but increased respiratory demands and periods of intermittent hypoxia probably play an important role.

Secondary outcomes are weight SDS at 12 months corrected age, height and head circumference SDS at 6 and 12 months corrected age, rate of rehospitalisations, respiratory symptoms (including wheezing, dyspnoea, exercise induced symptoms), unscheduled healthcare visits, (progression of) ROP, infant temperament (IBQ-R), quality of life of caregivers (CarerQoL) and cost-effectiveness.

In a subgroup of infants, additional secondary outcomes are lung function (lung clearance index), lung structure as assessed with chest CT scan and pulmonary hypertension and/or right ventricular systolic function as assessed with echocardiography at the corrected age of 6 months. These examinations are part of the standard of care.
protocol in some of the outpatient follow-up programmes in the Netherlands.

Data collection and management

For data management, Castor EDC will be used: a password protected, electronic database. Baseline characteristics including gestational age, birth weight, gender, pregnancy complications such as pre-eclampsia, past illnesses and ROP will be recorded in the database at inclusion by the local research team. SpO₂ data will be entered into the database by the central research team. Data from follow-up visits will be entered by the research team of the responsible NICU, as outpatient follow-up takes place in those centres. In case of missing data, every attempt will be undertaken to retrieve the data by contacting the respective hospitals.

Collected data will be pseudonymised and coded with a unique number, complying with the European General Data Protection Regulation. The key to link participants with their data will only be accessible to the local PI of the centre of inclusion and PI of the associated NICU. Data will be stored securely and will be saved for 15 years according to national legislation. Only central study investigators will have access to all collected data.

Patient and public involvement

Parents of children with BPD and several patient associations (Lung Foundation Netherlands, European Lung Foundation and the Neonatal Parents Organization (Care4Neo)) were involved in the development of the trial. In addition, parents of preterm born infants are part of the Advisory Board of the trial. They provide their experience in improving patient information material, publications and presentations for layman and will help with implementation after finalisation of the study.

Sample size estimation

A simulation study with four scenarios was performed to estimate the sample size needed with weight SDS at 6 months of corrected age as primary outcome. We assumed a mixed effects model with a random intercept to account for the correlation between the patients from the same hospital. We assumed 10 clusters (10 NICU centres with post-IC/HC departments in the surrounding regional hospitals) with each cluster having 16 (±3) or 18 (±3) patients. The mean weight at 6 months for the group with a lower saturation limit of 90% was assumed −1.15 SD (data from BPD cohort Erasmus MC, Rotterdam, the Netherlands, data on file). The mean weight at 6 months for the group with a lower saturation limit of 95% was assumed −0.65 SD, since a 0.5 SDS higher weight was considered clinically relevant. The variation in weight due to differences between individuals was assumed 1.18 SD, while the variation in weight due to differences between hospitals was assumed 0.10 and 0.20 SD. The scenario with the highest power (0.83) and greatest variation of weight between the various hospital clusters (0.20 SD) was chosen. This scenario leads to a sample size of 180 patients. Accounting for a dropout rate of 10%, we aim to include 198 infants.

Statistical analysis

Analyses will be performed on an intention-to-treat (ITT) basis. The ITT population will include all randomised infants, regardless of protocol deviations.

Comparison between the two groups for the primary endpoint will be made using a mixed effect model with a random intercept to account for the correlation between patients from the same hospital cluster. All secondary parameters will be assessed by linear mixed effect models for continuous outcomes or logistic mixed effect models for binary outcomes. BPD severity and weight at inclusion are considered relevant variables for the outcome weight SDS at 6 months. For the secondary analysis, these variables will be included in the mixed model analysis as fixed effects. Significance levels will be 0.05.

Missing values in the baseline covariates, if >10%, will be assumed to be missing at random and multiple imputations will be used. We do expect less than 10% missing data for the primary endpoint, weight SDS.

All analyses will be completed with the statistical software package R (www.rproject.org), and SPSS/PC Statistics V.21.0 (SPSS, Chicago, Illinois, USA).

Cost-effectiveness analysis

A trial-based economic evaluation will be used as a cost-effectiveness analysis performed from a societal perspective as well as from a healthcare perspective. The initial time horizon is 1 year. Costs will be calculated based on patient-level data on resource use inside and outside the healthcare sector during the first year of life of the infant. If an oxygen weaning strategy leads to better health outcomes at higher costs, incremental cost-effectiveness ratios will be calculated. Depending on which treatment is more effective, these ratios will express the additional costs per unit of health gain or the savings per unit of health forgone.

Although it is very plausible that health effects and differences in costs persist or occur later in life, currently available data and literature do not allow a meaningful extrapolation after the study period. Nevertheless, the children will be followed until the age of 8 years, outside of the scope of this initial study, according to national follow-up guidelines for preterm born children. This will make it possible to track costs and effects in the longer term.

ETHICS AND DISSEMINATION

Ethical consideration

Ethical approval for the trial has been obtained from the Medical Ethics Review Committee of the Erasmus University Medical Center, Rotterdam, the Netherlands (MEC-2018-1515). Local approval for conducting the trial in the participating hospitals has been or will be obtained from the local institutional review boards. Written informed
consent will be obtained from the parents or legal guardians of all study participants, adhering the Good Clinical Practice guideline. Protocol modifications will be communicated to all relevant parties.

Safety reporting and auditing
All SAE will be reported to the approving ethics committee in accordance with national guidelines. SAEs will be collected and recorded from informed consent signature to 2 weeks after stopping supplemental oxygen. After this period until the last follow-up visit at 12 months corrected age, only intensive care admissions for complicated respiratory tract infections and death will be considered SAEs and will be reported as such.

All participating sites will be audited by an independent study monitor. For frequency and procedures, see online supplemental file 5.

Data and Safety Monitoring Board
A Data and Safety Monitoring Board (DSMB) is installed. Although this study does not add extra risks to the safety of the patients, the DSMB is installed because of the vulnerability of the population and complicated logistics of a multicentre trial. The DSMB will monitor the safety, validity and credibility of the trial in order to protect the patients, but not futility. In principle, the trial will not be stopped early for a beneficial effect on the primary outcome. Safety analyses will be performed when approximately 25%, 50% and 75% of patients have reached the end of the follow-up (12 months corrected age). The data analysis will include ROP and SAE. The DSMB is independent from the sponsor; the committee members have declared no competing interests.

Dissemination
Results of the trial will be published in open-access journals. After ending of the trial and publication of results, the data collection of this trial will be available for sharing under conditions, through a secured, online portal (DANS).

Trial status
Patient inclusion was started in January 2020, but was temporarily paused due to regulations during the Corona virus pandemic (COVID-19). Inclusion restarted in August 2020.

Author affiliations
1 Department of Paediatrics/Paediatric Respiratory Medicine, Erasmus MC Sophia Children Hospital, Rotterdam, The Netherlands
2 Department of Paediatrics, Division of Neonatology, Amsterdam UMC Locatie AMC, Amsterdam, The Netherlands
3 Department of Paediatrics, Division of Neonatology, Amsterdam UMC Locatie VUMc, Amsterdam, The Netherlands
4 Department of Paediatrics, Division of Paediatric Pulmonology and Allergology, UMCG, Groningen, The Netherlands
5 Department of Biostatistics, Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands
6 Department of Paediatrics, Division of Neonatology, UMCG, Groningen, The Netherlands
7 Erasmus School of Health Policy and Management, Erasmus Universiteit Rotterdam, Rotterdam, The Netherlands
8 Department of Paediatrics, Amphia Hospital, Breda, The Netherlands
9 Department of Paediatrics, Division of Neonatology, Erasmus MC Sophia Children Hospital, Rotterdam, The Netherlands
10 Department of Paediatrics, Haga Hospital, Den Haag, The Netherlands

Collaborators

Contributors
MP, Ahvk, WD, DHN, EJL, EVH, PHD, AFB, AAK, IMKR and SB constitute the trial steering committee. MP, Ahvk, WD, DHN, EJL, EVH, PHD, AFB, AAK and IMKR designed the trial and will provide clinical expertise in the conduct of the trial. MP is the chief investigator and has overall leadership of the trial. DHN is partly responsible for logistical coordination of the trial. SB is responsible for overall coordination of the trial and management of the clinical data. ARR and AJS constitute the Advisory Board and provide clinical expertise in the conduct of the trial. LG is responsible for cost-effectiveness analyses. E-RA is the trial statistician. The SOS BPD study group consists of all local investigators in the participating hospitals who are responsible for patient recruitment and data collection. SB wrote the first draft version of the manuscript. All authors, including the study group, reviewed draft versions and approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Funding
This work was supported by the Lung Foundation Netherlands under grant number 4.1.17.162 and by Netherlands Organisation for Health Research and Development (ZonMW)—Efficiency Studies Programme under grant number B43 002 827.

Disclaimer
The study funders were not involved in the design of the trial and are not involved in data collection, analysis and interpretation of data.

Competing interests
None declared.

Patient and public involvement
Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication
Not applicable.

Provenance and peer review
Not commissioned; externally peer reviewed.

Supplemental material
This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access
This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

ORCID iD
Stephanie Balink http://orcid.org/0000-0002-3345-4397

REFERENCES


37 Data Archiving and Networking Services (DANS). Dutch national centre of expertise and repository for research data. Available: https://dans.knaw.nl/en