

Guidelines to analyse preclinical studies using perinatal derivatives

**Salomé Pires¹, Sveva Bollini², Maria Filomena Botelho¹, Ingrid Lang-Olip³,
Peter Ponsaerts⁴, Carolina Balbi^{5,6}, Anna Lange-Consiglio⁷, Mathilde Fénelon^{8,9},
Slavko Mojsilović¹⁰, Ekaterine Berishvili¹¹, Fausto Cremonesi⁷, Maria Gazouli¹²,
Diana Bugarski¹⁰, Alexandra Gellhaus¹³, Halima Kerdjoudj¹⁴, Andreina Schoeberlein^{15,16*}**

¹ Biophysics Institute, Faculty of Medicine, University of Coimbra; Coimbra, Portugal

² Department of Experimental Medicine (DIMES), University of Genova, Genova, Italy

³ Division of Cell Biology, Histology, Embryology, Gottfried Schatz Research Center, Medical University of Graz, Graz, Austria

⁴ Laboratory of Experimental Hematology, Vaccine and Infectious Disease Institute (Vaxinfectio), University of Antwerp, Wilrijk, Belgium

⁵ Laboratory of Cellular and Molecular Cardiology, Istituto Cardiocentro Ticino, Lugano, Switzerland

⁶ Center for Molecular Cardiology, University of Zurich, Zurich, Switzerland

⁷ Università degli Studi di Milano, Department of Veterinary Medicine and Animal Science (DIVAS), Lodi, Italy

⁸ Univ. Bordeaux, INSERM, BIOTIS, U1026, F-33000 Bordeaux, France

⁹ CHU Bordeaux, Service de chirurgie orale, F-33076 Bordeaux, France

¹⁰ Institute for Medical Research, University of Belgrade, Belgrade, Serbia

¹¹ Laboratory of Tissue Engineering and Organ Regeneration, University of Geneva, Geneva, Switzerland

¹² Department of Basic Medical Sciences, Laboratory of Biology, Faculty of Medicine, School of Health Science, National and Kapodistrian University of Athens, Athens, Greece

¹³ Department of Gynecology and Obstetrics, University Hospital Essen, University of Duisburg-Essen, Essen, Germany

¹⁴ Université de Reims Champagne Ardenne, EA 4691 Biomatériaux et Inflammation en site osseux, UFR d'odontologie, Reims, France

¹⁵ Department of Obstetrics and Feto-maternal Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

¹⁶ Department for BioMedical Research (DBMR), University of Bern, Bern, Switzerland

*** Correspondence:**

Andreina Schoeberlein

andreina.schoeberlein@dbmr.unibe.ch

Abstract

The last 18 years have brought an increasing interest in the therapeutic use of perinatal derivatives (PnD). Preclinical studies used to assess the potential of PnD therapy include a broad range of study designs. The COST SPRINT Action (CA17116) aims to provide systematic and comprehensive reviews of preclinical studies for the understanding of the therapeutic potential and mechanisms of PnD in diseases and injuries that benefit from PnD therapy.

Here we describe the publication search and data mining, extraction, and synthesis strategies employed to collect and prepare the published data selected for meta-analyses and reviews of the efficacy of PnD therapies for different diseases and injuries. A coordinated effort was made to prepare the data suitable to make statements for the treatment efficacy of the different types of PnD, routes, time points and frequencies of administration, and the dosage based on clinically relevant effects resulting in clear increase, recovery or amelioration of the specific tissue or organ function. According to recently proposed guidelines, the harmonization of the nomenclature of PnD types will allow for the assessment of the most efficient treatments in various disease models. Experts within the COST SPRINT Action (CA17116), together with external collaborators, will do the meta-analyses and reviews using the data prepared with the strategies presented here in the relevant disease or research fields. Our final aim is to provide standards to assess the safety and clinical benefit of PnD and to minimize redundancy in the use of animal models following the 3R principles for animal experimentation.

Keywords:

perinatal derivatives, preclinical studies, animal models, meta-analysis, database search, consensus, protocol

1 Introduction

Perinatal Derivatives (PnD) have been widely recognized as therapeutic tools for tissue engineering and regenerative medicine applications in a broad field of diseases or injuries in the past few years. The term PnD includes birth-associated tissues obtained from term placentas and fetal annexes in their naïve or processed form such as the amniotic and chorionic membranes, chorionic villi, the umbilical cord, the basal plate, and the amniotic fluid, as well as the cells isolated from these tissues and the factors released by them (such as free nucleic acids, soluble proteins, lipids, extracellular vesicles or extracellular matrix components) (Silini et al., 2020). Preclinical studies are an essential milestone on the road to clinical translation. There has been extensive research using PnD therapy in animal models, and publications describing *in vivo* preclinical studies using PnD have shown annual increases in the last 10-15 years. The perinatal derivatives studied are diverse regarding donor population, tissue source, isolation, expansion, and storage protocols. The study designs are equally heterogeneous: even for the same target disease, outcome measures include various parameters and are often evaluated at different time points (Aziz et al., 2019). Therefore, it is unclear which types of PnD provide optimal therapeutic results, when and how they are best applied, and which are the underlying mechanistic effects of therapy using PnD.

The International Network for Translating Research on Perinatal Derivatives into Therapeutic Approaches (SPRINT, CA17116¹), funded by COST (European Cooperation in Science and Technology²), is an initiative to bridge the gaps between PnD research and their translation into the clinic. Specifically, the SPRINT working group dedicated to preclinical studies aims to collect and critically analyze preclinical data to provide a clear understanding of the therapeutic potential for specific pathological conditions and the underlying mechanisms in different *in vivo* models. Systematic and comprehensive reviews of preclinical studies will identify research gaps for each animal model and the disease of interest and evaluate therapeutic PnD interventions' efficacy. SPRINT will focus on PnD applications involving differentiation capabilities into tissue-specific cells or paracrine actions via the release of mediating factors acting on resident and progenitor cells, in line with the body of published benefits in animal models of acute injury and chronic inflammatory diseases. The analysis of the included studies will be made public to foster the consensus on the proper study designs, the knowledge of the therapeutic efficacy of PnD, and – last but not least – to minimize redundancy in animal experimentation in line with the Replacement, Reduction, and Refinement (3R) principles for more ethical use of animals in research (Russell and Burch, 1959).

The COST SPRINT Action (CA17116) recently published a consensus paper on the human placenta tissue and cell nomenclature (Silini et al., 2020). The focus of the SPRINT reviews of animal models for different diseases and injuries is set on assessing the studies for a clear definition of the research question in terms of population, interventions, comparators, outcomes, and study designs (PICOS) (McKenzie et al., 2021). Accurate description and characterization of the PnD used in animal studies are often suboptimal, and the naming and abbreviations of the PnD types at the authors' discretion. In the reviews published by the SPRINT consortium, the naming of the

¹ <https://www.sprint-cost.org/>

² <https://www.cost.eu/>

PnD types used in the animal studies will be harmonized according to the proposed nomenclature for improved comparability.

2 Methods used to collect the data

The SPRINT preclinical studies working group defined a common approach to facilitate and coordinate the collection of published data to be included in the planned disease- or research field-specific reviews. A workflow following the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021a; Page et al., 2021b) was defined as described below.

2.1 Search strategy and data mining

A systematic literature search of the PubMed® database (2020b) was performed and updated on February 22, 2022. After reaching consensus following an open discussion with all SPRINT members, the Boolean search string was designed to maximize the inclusiveness of publications for PnD. With the same scope in mind, additional preclinical search terms for animal models were included (**Figure 1A**). We excluded non-original research as well as studies using umbilical cord blood or hematopoietic cells from the search string.

2.2 Selection of studies and inclusion criteria

The database records identified using the search string were then imported into a Mendeley publication library shared with all COST SPRINT Action members and accessible online or via a locally installed application (Mendeley Desktop version 1.19.8 or Mendeley Reference Manager version 2.66.0, Elsevier B.V. Amsterdam, The Netherlands³). Eligible studies were selected following a workflow compliant with the PRISMA guidelines, as outlined in **Figure 1B**. Briefly, more than 12'000 publications were imported into the publication library and assigned to working group members based on the year of publication to verify the inclusion criteria: In the first selection round, the key inclusion criteria were PnD treatments in *in vivo* models and the evaluation of their efficacy. Only original research studies available as a full text in English were included. In the early years of PnD research, only a few studies were published that met the inclusion criteria, and the definition of PnD was often not accurate or well defined. Therefore, the time frame was restricted to publication years 2004-February 22, 2022 (**Figure 2**). A total of 2'259 publications were initially classified as eligible. The aim of the SPRINT preclinical studies working group was to identify diseases or research fields that benefit from PnD therapy. The working group identified diseases or research fields where its members have the necessary expertise to define appropriate outcome measures and judge the eligibility of the studies. The research fields covered by the SPRINT preclinical studies working group include cardiovascular repair and regeneration, neuroprotection and regeneration, in utero prenatal therapy, diabetes or metabolic syndrome, inflammation- and immune-related diseases, oncology, reproduction, bone regeneration, and wound healing. All eligible studies were classified into the defined research fields by the working group leaders. Preclinical working group members with the necessary expertise verified and

³ <https://www.mendeley.com/>

confirmed or excluded all studies allocated to their respective research fields for the final selection of relevant studies to be included in the meta-analyses. The selection of relevant studies was based on the availability of data from functional tests that mark the current state-of-the-art for assessing therapeutic effects in the respective disease or research field and are significant for the translation of the results into clinical practice.

2.3 Data management

A master relational database (Microsoft Access, Microsoft Corporation, Redmond, WA, United States of America) including data fields for bibliometric data, publication metrics, and the studies' experimental data was established (**Figure 1C**). A Microsoft Excel (Microsoft Corporation) table template representing the same structure and data field formats was provided to all working group members to be filled in with the studies selected in their disease or research fields. Selected publications were either directly imported into the database or from the Microsoft Excel tables. The use of the PubMed identifier (PMID) as a unique identifier allowed for the exclusion of duplicates. The entries were also checked for published corrections to update the original entries and for editorials relating to original studies that were excluded. Publication metrics were used as informational selection criteria to help identify highly cited publications but did not result in the exclusion of publications. InCites Journal Citation Reports⁴ (Clarivate, 2020) were consulted to retrieve the journal publication metrics, while iCite⁵ (National Institutes of Health, Bethesda, MD, United States of America) (Hutchins et al., 2016; Hutchins et al., 2017; Hutchins et al., 2019a; Hutchins et al., 2019b) and Dimensions⁶ (Digital Science & Research Solutions Inc., London, United Kingdom) (Hook et al., 2018; 2020a) served for the inclusion of the studies' individual publication metrics.

2.4 Data extraction

The extraction of the experimental data from the selected studies is currently on-going. For each disease or research field, the experimental data from the selected publications are extracted by working group members or external collaborators with the respective expertise (**Figure 1C**). If applicable, established naming of the animal models and outcome measures are used. To adhere to the population, interventions, comparators, outcomes, and study designs (PICOS) criteria (McKenzie et al., 2021), the recipient (animal) and donor (human or animal) populations are recorded in all details available. Since the analysis of the studies is centered around PnD as the primary intervention, the PnD type and the degree of characterization prior to their administration is registered as published. In a second stage, the PnD type is named according to the proposed consensus nomenclature for PnD (Silini et al., 2020) to allow for a comparison of their treatment efficacies. The control and experimental groups, including the treatment modalities (vehicle/sham treatment for controls, dosage, single/multiple administrations, time point(s), and route(s) of administration), are described. The primary and secondary outcome measures are noted in conjunction with the respective follow-up period(s) and the time point(s) of analysis. If outcome measures were reported in a graphical format only, the data represented in diagrams are digitized

⁴ <https://jcr.clarivate.com/>

⁵ <https://icite.od.nih.gov/>

⁶ <https://app.dimensions.ai/discover/publication>

using open resource image processing applications such as WebPlotDigitizer⁷ (Rohatgi, 2020). The statistical tests used in the studies are also recorded in the master database.

2.5 Data synthesis

Systematic reviews are carried out to assess the treatment efficacy and the clinical benefit of PnD by comparing the outcomes measured in clinical scores in non-treated *versus* treated animals, when possible (**Figure 1D**). All types of PnD used in a specific disease model are compared to indicate the suitability of the different PnD types as a treatment for a given disease or injury. Likewise, the routes of administration, the dosages, and the frequency of administration are compared by measuring the differences in clinical scores as a readout for improvement. The quality of preclinical studies is typically rather heterogeneous. Therefore, a risk of bias assessment is evaluated using tools such as the SYRCLE's risk of bias tool for animal studies (Hooijmans et al., 2014), the revised Cochrane's risk of bias evaluation tool (RoB-2) (Sterne et al., 2019) or ROBINS-I tool for non-randomized studies (Sterne et al., 2016) to indicate low, high or unclear risk of bias for the description of the host animals' characteristics, randomization process, blinding of group allocation and outcome measurement and completeness of outcome data reporting (Kassem and Kamal, 2020; Maltais-Bilodeau et al., 2021).

3 Discussion

It is the aim of the International Network for Translating Research on Perinatal Derivatives into Therapeutic Approaches (SPRINT, CA17116) to provide independent and scientifically sound knowledge and guidelines to foster the safe and efficient therapeutic use of PnD. To our knowledge, a systematic review of preclinical studies comparing all types of PnD for a variety of diseases and research fields has not been conducted to date. To validate future therapies, animal models are still widely regarded as the gold standard for the evaluation of therapies in diseases with a multifactorial pathology or involving complex organs. The meta-analysis of preclinical studies contributes to the 3R principle and will, therefore, have long-term social and ethical impacts. To further improve the long-term use of future preclinical studies, we recommend filling out the Compliance Questionnaire provided by the Animal Research: Reporting of In Vivo Experiments (ARRIVE, <https://arriveguidelines.org/>) guidelines (Percie du Sert et al., 2020).

The host animal breed or strain (including information on mutant alleles and immune status) is generally well documented, but information on the human donor ethnicity, age, gestational age etc., is often missing or not well described. While the collection of PnD tissue under an anonymized donation scheme without disclosure of personal data is compliant with the Code of Ethics, the documentation of general patient-related data as stated above would be beneficial for future meta-analyses taking these parameters into account.

Obviously, there is a significant amount of variability between diseases for the choice of primary and secondary experimental outcome measures. Within research fields, there is often a broad spectrum of analytical and behavioral tests used to assess the efficacy of the treatments. Well-defined and standardized animal models are required to compare outcome measures between

⁷ <https://automeris.io/WebPlotDigitizer/>

studies. Human diseases and injuries come in various distinct subtypes, while animal models often represent only the pathologies' primary aspect(s). Preclinical models designed for the best possible representation of the human disease might deviate from the standard models that would allow for an adequate meta-analysis of different treatments. This conflict of interest is challenging to overcome. General statements made for the treatment efficacy of types of PnD, routes, time points and frequencies of administration, and dosages might hold true for standardized models but have to be carefully reevaluated to find the best treatment for a specific pathology or patient population. Nevertheless, the International Network for Translating Research on Perinatal Derivatives into Therapeutic Approaches (SPRINT, CA17116) firmly believes that in the future, therapeutic applications of PnD and the knowledge gain of their therapeutic potential and underlying mechanisms will clearly profit from an in-depth, comprehensive, and evidence-based analysis of all data available from basic science, preclinical, and clinical studies.

4 Data Availability Statement

Access to the publication libraries will be granted on justified request.

5 Author Contributions

SP, SB, MFB, ILO, PP, CB, ALC, MF, SM, EB, FC, DB and AS analysed the data. AS drafted the manuscript. SP, SB, MFB, ILO, ALC, MF, SM, EB, MG, AG, HK, MR and AS contributed to revising and editing the article and all authors approved the submitted version.

6 Funding

This work was supported by: University of Genova, *Curiosity Driven Grant "Triggering CARDIOmyocyte renewal by harnessing the STem cell pARacrine potential (CARDIO-STAR)"* to Sveva Bollini and by the University of Geneva, Horizon 2020 Framework Program (VANGUARD 874700) to Ekaterine Berishvili.

7 Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

8 Acknowledgments

This article is based upon work from COST Action CA17116 "International Network for Translating Research on Perinatal Derivatives into Therapeutic Approaches (SPRINT)", supported by COST (European Cooperation in Science and Technology).

9 References

- Aziz J, Liao G, Adams Z, Rizk M, Shorr R, Allan DS (2019). Systematic review of controlled clinical studies using umbilical cord blood for regenerative therapy: Identifying barriers to assessing efficacy. *Cytotherapy*. 21:1112-1121. doi: [10.1016/j.jcyt.2019.08.004](https://doi.org/10.1016/j.jcyt.2019.08.004)
- Dimensions. Digital Science & Research Solutions Inc., London, United Kingdom (2020). <https://app.dimensions.ai/discover/publication> [Accessed December 11, 2020]
- InCites Journal Citation Report. Clarivate, Boston, MA, United States of America (2020). <https://jcr.clarivate.com/> [Accessed December 11, 2020]
- Hooijmans CR, Rovers MM, de Vries RB, Leenaars M, Ritskes-Hoitinga M, Langendam MW (2014). SYRCLE's risk of bias tool for animal studies. *BMC Med. Res. Methodol.* 14:43. doi: [10.1186/1471-2288-14-43](https://doi.org/10.1186/1471-2288-14-43)
- Hook DW, Porter SJ, Herzog C. (2018). Dimensions: Building Context for Search and Evaluation. *Front. Res. Metr. Anal.* 3:23. doi: [10.3389/frma.2018.00023](https://doi.org/10.3389/frma.2018.00023)
- Hutchins BI, Baker KL, Davis MT, Diwersy MA, Haque E, Harriman RM, Hoppe TA, Leicht SA, Meyer P, Santangelo GM (2019a). The NIH Open Citation Collection: A public access, broad coverage resource. *PLoS Biol.* 17:e3000385. doi: [10.1371/journal.pbio.3000385](https://doi.org/10.1371/journal.pbio.3000385)
- Hutchins BI, Davis MT, Meseroll RA, Santangelo GM (2019b). Predicting translational progress in biomedical research. *PLoS Biol.* 17:e3000416. doi: [10.1371/journal.pbio.3000416](https://doi.org/10.1371/journal.pbio.3000416)
- Hutchins BI, Hoppe TA, Meseroll RA, Anderson JM, Santangelo GM (2017). Additional support for RCR: A validated article-level measure of scientific influence. *PLoS Biol.* 15:e2003552. doi: [10.1371/journal.pbio.2003552](https://doi.org/10.1371/journal.pbio.2003552)
- Hutchins BI, Yuan X, Anderson JM, and Santangelo GM. (2016). Relative Citation Ratio (RCR): A new metric that uses citation rates to measure influence at the article level. *PLoS Biol.* 14:e1002541. doi: [10.1371/journal.pbio.1002541](https://doi.org/10.1371/journal.pbio.1002541)
- Kassem DH, Kamal MM (2020). Therapeutic efficacy of umbilical cord-derived stem cells for diabetes mellitus: a meta-analysis study. *Stem Cell Res. Ther.* 11:484. doi: [10.1186/s13287-020-01996-x](https://doi.org/10.1186/s13287-020-01996-x)
- Maltais-Bilodeau C, Henckel E, Cobey KD, Ahmadzai N, Skidmore B, Ferretti E, Thébaud B (2021). Efficacy of Mesenchymal Stromal Cells in Preclinical Models of Necrotizing Enterocolitis: a Systematic Review Protocol. *Research Square* [Preprint]. doi: [10.21203/rs.3.rs-239448/v1](https://doi.org/10.21203/rs.3.rs-239448/v1)
- McKenzie JE, Brennan SE, Ryan RE, Thomson HJ, Johnston RV, Thomas J (2021). "Chapter 3: Defining the criteria for including studies and how they will be grouped for the synthesis". In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022)*, Cochrane (2022). <https://training.cochrane.org/handbook/current/chapter-03> [Accessed February 22, 2021]
- Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC,

Welch VA, Whiting P, Moher D (2021a). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 372:n71. doi: [10.1136/bmj.n71](https://doi.org/10.1136/bmj.n71)

Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, McKenzie JE. (2021b). PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ* 372:n160. doi: [10.1136/bmj.n160](https://doi.org/10.1136/bmj.n160)

Percie du Sert N, Hurst V, Ahluwalia A, Alam S, Avey MT, Baker M, Browne WJ, Clark A, Cuthill IC, Dirnagl U, Emerson M, Garner P, Holgate ST, Howells DW, Karp NA, Lazic SE, Lidster K, MacCallum CJ, Macleod M, Pearl EJ, Petersen OH, Rawle F, Reynolds P, Rooney K, Sena ES, Silberberg SD, Steckler T, Würbel H. (2020). The ARRIVE guidelines 2.0: Updated guidelines for reporting animal research. *PLoS Biol.* 18:e3000410. doi: [10.1371/journal.pbio.3000410](https://doi.org/10.1371/journal.pbio.3000410)

PubMed. US National Library of Medicine, National Institutes of Health, Bethesda MD, United States of America (2020b). <http://www.ncbi.nlm.nih.gov/pubmed> [Accessed February 22, 2022].

Rohatgi, A. (2020). WebPlotDigitizer, version 4.4. (Pacifica, CA, United States of America). <https://automeris.io/WebPlotDigitizer> [Accessed December 11, 2020]

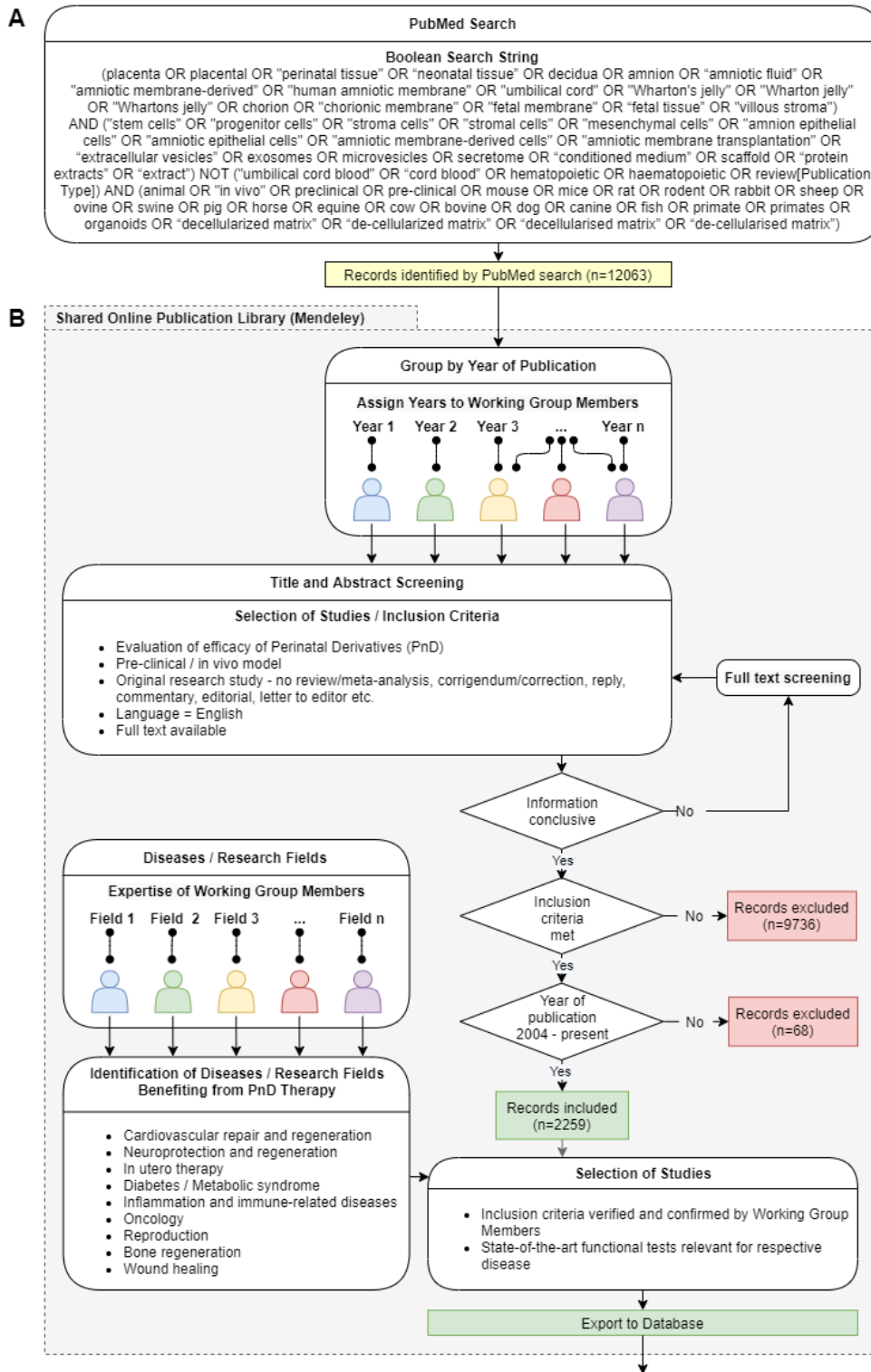
Russell WMS, Burch RL (1959). *The Principles of Humane Experimental Technique*. London, UK: Methuen & Co. Limited

Silini AR, Di Pietro R, Lang-Olip I, Alviano F, Banerjee A, Basile M, Borutinskaite V, Eissner G, Gellhaus A, Giebel B, Huang Y-C, Janev A, Erdani Kreft M, Kupper N, Abadía-Molina AC, Olivares EG, Pandolfi A, Papait A, Pozzobon M, Ruiz-Ruiz C, Soritau O, Susman S, Szukiewicz D, Weidinger A, Wolbank S, Huppertz B, Parolini O (2020). Perinatal Derivatives: Where Do We Stand? A Roadmap of the Human Placenta and Consensus for Tissue and Cell Nomenclature. *Front. Bioeng. Biotechnol.* 8:1438. doi: [10.3389/fbioe.2020.610544](https://doi.org/10.3389/fbioe.2020.610544)

Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan A-W, Churchill R, Deeks JJ, Hróbjartsson A, Kirkham J, Jüni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Schünemann HJ, Shea B, Shrier I, Tugwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA, Whiting PF, Julian Pt Higgins JP (2016). ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 355:i4919. doi: [10.1136/bmj.i4919](https://doi.org/10.1136/bmj.i4919)

Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng H-Y, Corbett MS, Eldridge SM, Emberson JR, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT (2019). RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 366:l4898. doi: [10.1136/bmj.l4898](https://doi.org/10.1136/bmj.l4898)

10 Figures



(continued on next page)

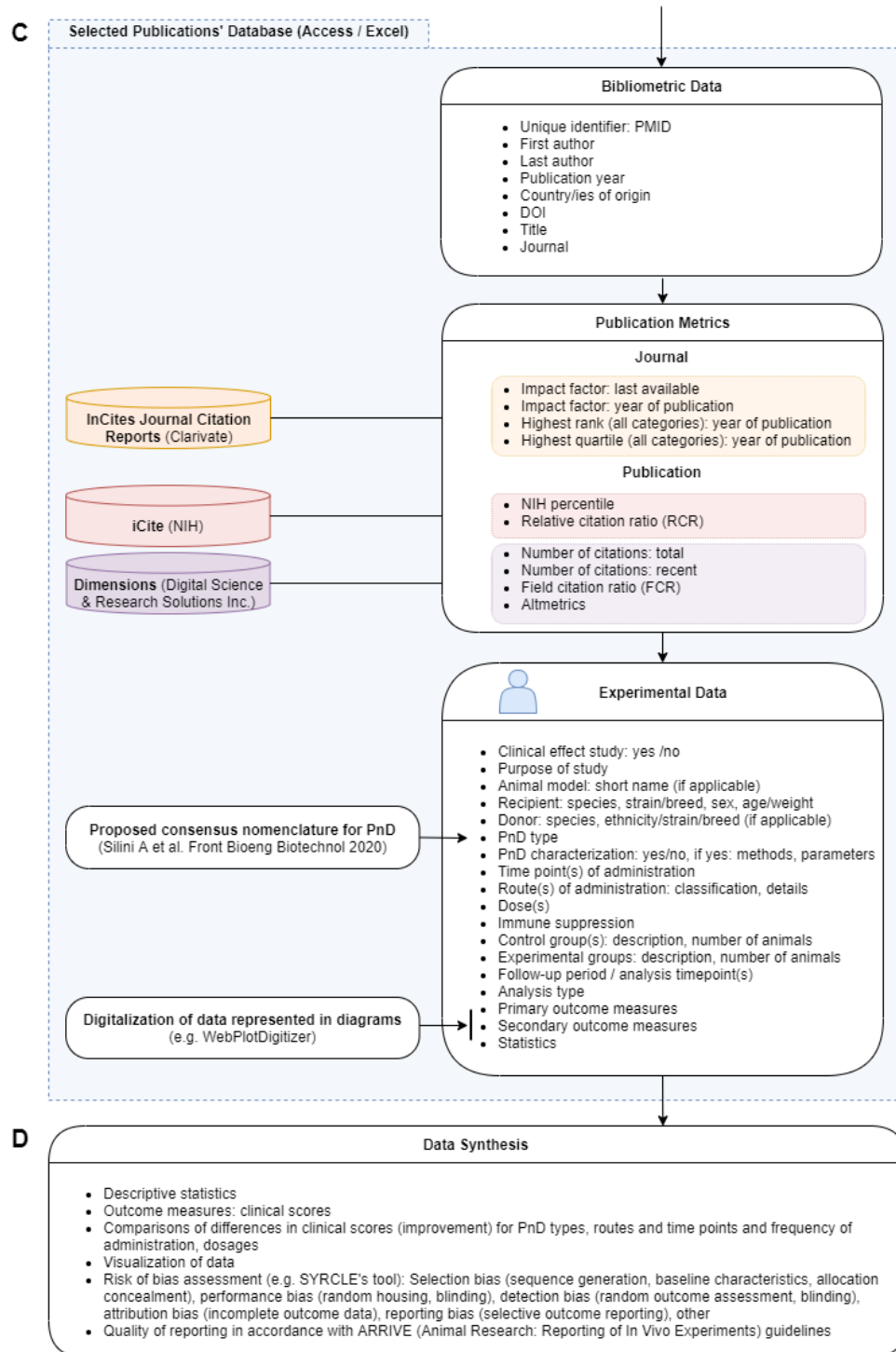


Figure 1. Boolean search string used to identify preclinical studies using Perinatal Derivatives (PnD) as a therapeutic approach (A). Workflow for the selection of studies using the internally shared Mendeley publication library (B). Workflow for the data collection of selected studies indicating data containers for publication metrics, nomenclature guideline and data digitalization tool (C). Common denominators for the meta-analyses in the different research fields (D).

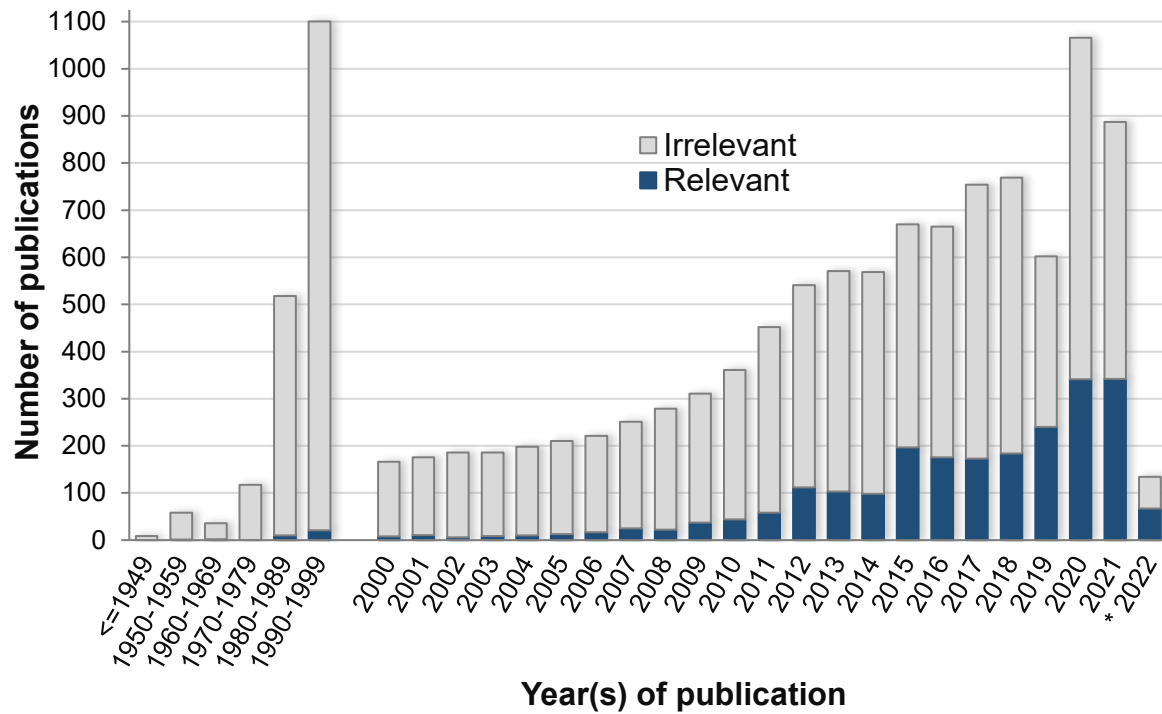


Figure 2. Number of publications identified in PubMed through the Boolean search string (see Figure 1A) and classified into relevant (meeting inclusion criteria, dark blue boxes) vs. irrelevant (excluded studies, light grey boxes), by decade or year of publication. Records starting from 2004 were considered for inclusion in the database. *2022 includes publications until February 22, 2022.