Study protocol (Version 1.2, January 2019):

Impact of Cervical Pessary Treatment for Prevention of Preterm Birth in Twin Pregnancies with Cervical Shortening on children`s Long-Term Survival without Neurodevelopmental Disability: *THE IMPETUS TRIAL*

Ioannis KYVERNITAKIS[1,2], Eva HERRMANN[3], Holger MAUL[4], Lars HELLMEYER[5], Amr HAMZA[6], Andreas NONNENMACHER[7], Wolfgang HENRICH[7], Daniela REITZ[8], Bettina KUSCHEL[9], Johannes STUBERT[10], Jens STUPIN[7], Apostolos ATHANASIADIS[11], George DASKALAKIS[12], Sven SCHIERMEIER[13], Richard BERGER[14], Marita WASENITZ[1], Ekkehard SCHLEUSSNER[15], Zarko ALFIREVIC[16], Ben Willem MOL[17] and Franz BAHLMANN[1]

[1] Dpt. Of Obstetrics and Gynecology, Buergerhospital and Clementine Kinderhospital Frankfurt a.M.,
Dr. Senckenberg Foundation and Johann-Wolfgang-Goethe University of Frankfurt
janniskyvernitakis@gmail.com, m.wasenitz@buergerhospital-ffm.de, f.bahlmann@buergerhospital-ffm.de
[2]Faculty of Medicine, Philipps-University of Marburg
[3]Institute of Biostatistics and Mathematical Modelling, Goethe-University of Frankfurt, Faculty of Medicine, Frankfurt a. M., Germany
herrmann@med.uni-frankfurt.de
[4]Dpt. Of Obstetrics and Prenatal Medicine, Asklepios Kliniken Barmbek and Nord-Heidberg, Hamburg, Germany
h.maul@asklepios.com
[5]Dpt. Of Obstetrics and Prenatal Medicine, Vivantes Klinikum im Friedrichshain, Berlin, Germany
Lars.Hellmeyer@vivantes.de
[6]Dpt. Of Obstetrics and Prenatal Medicine, Universitätsklinikum des Saarlandes, Homburg, Germany
amr.hamza@uls.eu
[7]Dpt. of Obstetrics & Gynecology, Charité-Universitätsmedizin, Berlin, Germany
andreas.nonnenmacher@charite.de, wolfgang.henrich@charite.de, jens.stupin@charite.de
[8]Dpt. of Obstetrics & Gynecology, Klinikum Darmstadt GmbH, Germany
reitz.daniela@gmx.de
[9]Dpt. Of Obstetrics and Prenatal Medicine, MRI- Klinikum rechts der Isar, Germany
Bettina.Kuschel@mri.tum.de
[10]Dpt. of Obstetrics & Gynecoogyl, Universitätsfrauenklinik und Poliklinik am Klinikum Südstadt Rostock
[11]Dpt. of Obstetrics & fetal medicine, Medical School of the Aristotle-University of Thessaloniki, Greece
apostolos3435@gmail.com
[12]Dpt. of Obstetrics & Gynecoogyl, University Hospital of Athens, Greece
gdaskalakis@yahoo.com
[13]Dpt. Of Obstetrics and Gynecology, University Hospital of Witten and Herdecke, Witten, Germany
sven.schiermeier@elisabethgruppe.de
[14]Dpt. Of Obstetrics and Gynecology, Marienhospital Neuwied, Germany
Richard.Berger@marienhaus.de

[15]Dpt. Of Obstetric Medicine, University of Jena, Germany, ekkehard.schleussner@med.uni-jena.de
[16]Dpt. Of Women's and Childern's Health, University of Liverpool and Joint Coordinating Editor of the Cochrane Pregnancy and Childbirth
Zarko@liverpool.ac.uk
[17]Dpt. Of Obstetrics & Gynecology, Monash University, Australia
ben.mol@monash.edu

Correspondance to:

PD Dr. med. Ioannis Kyvernitakis

Dpt. Of Obstetrics and Gynecology

Buergerhospital and Clementine Childern's hospital Frankfurt/Main

Nibelungenallee 37-41

60318 Frankfurt/Main

T +49 69 1500 5807

Email: janniskyvernitakis@gmail.com

Abstract:

Background: Spontaneous preterm birth (SPB) is the most important cause for perinatal morbidity and mortality. Since women with a twin pregnancy are at increased risk of preterm delivery, interventions to prevent preterm birth are urgently needed.

Methods: This is a randomized controlled trial to investigate the effectiveness of cervical pessary in women with a twin pregnancy and shortened cervix on the short- and long-term neonatal outcome. The effectiveness of the cervical pessary treatment will be assessed at three different stages of the second trimester (16-20 (early) vs. 20-24 (middle) vs. 24-28 (late) weeks of gestation).

Women eligible for the study will undergo serial cervical length measurements and will be randomized and allocated to either pessary treatment or expectant management as soon as the cervical length is shortened below the 25th percentile of the reference values. The pessary will be left in situ until 37 completed weeks or earlier if necessary.

Primary outcome is the children`s long-term survival without neurodevelopmental disability at 3 years of corrected age. A key safety endpoint will include the composite neonatal outcome as well as preterm birth before 34 weeks. Secondary outcomes focus on the short-term outcome of mother and newborns. We will include 672 women in parallel groups (pessary vs. control group) each using 3 strata according to week of gestation. This will allow us to demonstrate or refute a 18.6% higher survival rate of children without neurodevelopmental disability at the age of 3 in the pessary-group (Cochran-Mantel-Haenszel test, alpha-error 5%, 80% power).

Discussion: We hope to confirm the results of the ProTwin*Kids*-Trial, which demonstrated a 18.6% higher survival rate of children without neurodevelopmental disability at the age of 3 in the pessary-group. We postulate that the survival without neurodevelopmental disability depends on the onset of cervical shortening and its treatment with a cervical pessary, respectively. This project is summarizing registered RCTs in twin pregnancies all using CORE^3 outcome parameters.

Trial Registration: ClinicalTrials.gov Identifier: NCT03418311. Registered on 23rd January 2018.

Keywords: Preterm Birth, Twin, Cervical length, Arabin Cervical Pessary, Children´s Long-Term Outcome

Background

Background and rational:

Preterm birth (PTB) complicates 13% of all pregnancies worldwide and is the most important cause of neonatal morbidity and mortality[1]. Women with a twin pregnancy are at increased risk of preterm delivery. Approximately 50% of women with a multiple pregnancy deliver before 37 weeks of gestation (WoG), of whom 9% deliver before 32 weeks[2]. The prevalence for multiple pregnancies is constantly increasing and reached 1.85% in 2015 in Germany[3].

Although disability-free survival rates have increased over the years as a result of improved facilities and treatments, preterm birth is still accountable for 75% of all perinatal deaths and >50% of morbidities[4,5]. Morbidity and mortality are inversely related to gestational age; of those infants born <30 weeks of gestation, only 25% are free of disabilities at the age of five years [5, 6] whereas only 8% of children born at 32 weeks of gestation have a risk for neurodevelopmental delay[7]. However, late preterm (> 32 WoG) neonates still have a 10-fold increased mortality risk as compared to neonates born at term[8].

Apart from the personal tragedies for those involved, sPTB generates immense healthcare costs[9]: The overall health care costs for premature babies differ dramatically by week of gestation at birth: after their first year of life the total health care costs summed up to 74.000 € for early premature (<28 WoG), to 8.565 € for late premature (28 WoG – 37 WoG) and to 1.590 € for full-term born children[10] in Germany. Evidence based treatment guidelines concerning prevention of sPTB are not available in Europe. Expectant management is still usual care[11] with interventions only in terms of a tertiary prevention of sPTB according to guidelines for premature rupture of membranes, premature labour or other pregnancy complications[12]. A short cervix (<25 mm) is associated with early and very early preterm birth in twins and 15% of women with twin gestations have a cervix ≤ 25 mm[13]. Therapeutic options like vaginal progesterone[14] and cervical cerclage[15] have been shown to be ineffective in reducing sPTB in twin pregnancies.

Cervical pessary treatment is a non-invasive, well-tolerated and cost-effective treatment option[16] for the prevention of sPTB. The available clinical trials for cervical pessary treatment in twin

pregnancies with a shortened cervix reflect contradicting results: the ProTwin[17] and PECEP-Twin trial[18] (N=267) demonstrated a significant reduction of sPTB. The clinical trial of Nicolaides et al. [19](N=214), however, reported no significant effect.

In view of these conflicting results, the Impetus trial is needed to establish evidence based therapeutic guidelines for the prevention of sPTB in women with a twin pregnancy with a shortened cervix. The study will assess the effectiveness of pessary placement as soon as the cervical shortening occurs. The Impetus Trial is a multicentre, open-label, randomised, controlled trial in parallel groups; it might be considered as part of the prospective meta-analysis conducted by the Global Obstetrics Network (Go-Net)[20].

Methods

Study setting

This is a multicenter study to be conducted in 6 hospitals in Germany and in 2 hospitals in Greece. All hospitals are academic hospitals providing an obstetrical department along with a tertiary perinatal unit.

Participating centres in Greece are: Medical School of the Aristotle-University of Thessaloniki, University Hospital of Athens and in Germany: Vivantes Klinikum im Friedrichshain Berlin, Charité-Universitätsmedizin Berlin, Asklepios Kliniken Hamburg, Universitätsklinikum des Saarlandes Homburg, Universitätsfrauenklinik und Poliklinik am Klinikum Südstadt Rostock, Klinikum Darmstadt, Klinikum rechts der Isar Technische Universität München. All participating centres will file their own EC approval.

The trial was registered on January 23rd in 2018 in ClinicalTrials.gov (https://clinicaltrials.gov/ct2/results?cond=&term=NCT03418311&cntry=&state=&city=&dist=); the trial number is NCT03418311.

Eligibility criteria:

Women presenting with a diamniotic twin pregnancy in week of gestation (WoG) 16 till 28 and a shortened cervix below the 25th percentile[21] are eligible for the study. Gestational age will be determined through menstrual history and first trimesters scan, cervical length (CL) will be measured by a transvaginal ultrasonography scan (US) according to a standard technique[22]. The measurements will be performed by experienced and trained maternal-fetal specialists.

Women with monoamniotic pregnancies or pregnancies complicated by suspected twin-to-twin transfusion syndrome, intrauterine death of one twin, major congenital abnormalities and uterine malformations will be excluded from the study. Women with active vaginal bleeding, spontaneous rupture of membranes, painful regular uterine contractions or a cervical cerclage in situ at the time of randomization will also be excluded. Silicone allergy and a current participation in another RCT are exclusion criteria as well. Women have to be older than 18 years and capable of giving informed consent.

Maintenance of the randomisation codes and test procedures of the trial.

Every participating centre will have its own randomisation list.

We have created a database in a website so it can be accessed worldwide, that every hospital will be able to randomize their patients. Every center will receive a password and a username in order to access the database for recruitment, randomization and documentation of patient data. Hereby, a personal identification number will be assigned for every patient. Patient names will not appear in the databases.

This database will be supervised and coordinated by Dr. Ioannis Kyvernitakis, Bürgerhospital Frankfurt/M. (Webmaster).

Identification of data to be collected in the case report files (CRF) that should be considered as data source.

Data will be collected in E-CRF, provided by >Dr. Olaf Hars Wissenschaft, Berlin< on study software “Castor”.

Definition of what is considered to be the end of the study.

The study will be finished after the 3 year-follow up examination concerning neurodevelopmental disabilities, which will be conducted on the surviving children of the participating patients.

Interventions:

Pessary-Group-participants will receive management as usual except for placement of the cervical pessary (non-invasive) at enrolment including a transvaginal ultrasound to verify its correct fit and removal of the cervical pessary (non-invasive) in a regular preventive examination at WoG 37. The Arabin cervical pessary will be used in this trial; it is CE-certified for preventing SPB (CE 0482 / EN ISO 13485: 2012 + AC: 2012 annex III of the council directive 93/42 EEC)[23]. Serial measurements of the cervical length should be performed every 4 weeks for all patients until removal of the pessary.

Further surveillance of the pregnancy will not be influenced by the participation in the study.

Women in the control group will receive management as usual; i.e. expectant management with interventions only in terms of a tertiary prevention of PTB according to guidelines for premature rupture of membranes, premature labour or other pregnancy complications[11]. As therapeutic options like vaginal progesterone[14] and cervical cerclage[15] have been shown to be ineffective in reducing sPTB in twin pregnancies no concomitant drug theray is permitted.

Outcomes

The primary outcome will be survival of the children without neurodevelopmental disability at 3 years of corrected age: neurodevelopmental disability is a common problem regarding preterm new-borns. As such, the core outcome of the Impetus trial is to assess not only the survival but also the neurological status of the children as implemented by the CROWN Initiative[24]. This outcome measure focuses on whether the surviving children will be impaired by a mental disability in life or not; the exact potential disability is not object of the study. Furthermore, a key safety endpoint will be preterm birth before 32+0 weeks as well as composite neonatal outcome.

Secondary outcomes will be related to the pregnancy, delivery and the short-term outcome of the neonates. The outcome measures for pregnancy and delivery will be: hospitalisation for threatened preterm labour (days hospitalisation, tocolytic treatment (type, days, dose); premature rupture of membranes (PROM); infection / inflammation; physical or psychological intolerance to pessary; rate of significant maternal adverse events (heavy bleeding, cervical tear due to pessary placement, uterine rupture); maternal death; preterm birth as rate of delivery before weeks of gestation: 36+6 / 33+6 / 31+6 / 29+6 / 27+6; time to birth; birth weight (g).

As short-term neonatal outcome will be assessed: fetal or neonatal death within the first 24 hours; neonatal morbidity as rate of major adverse neonatal outcomes before discharge from the hospital (intraventricular haemorrhage III-IV, retinopathy of prematurity, respiratory distress syndrome II-IV, need for ventilation > 72 h, necrotising enterocolitis, proven or suspected sepsis (antibiotics >5 days), need (days) for neonatal special care, harm from intervention.

Our outcome measures meet the core-outcome set for the evaluation of interventions to prevent PTB published by the crown-initiative in 2016[24].

Participant timelines

Fig 1

We expect patient recruitment to take approximately 2 years. The study duration of the entire trial is estimated to be 68 months, whereas the intervention duration for the clinical trial will take approximately 29 months and the intervention duration per patient max. 25 weeks.

Sample size

For sample size calculation, we account for the stratified design and assume three equally large gestation groups. For the pessary group, we assume a combined event rate of at least 8% for the primary outcome and for the comparison of the pessary group with the control group we assume an odds ratio of 2.29. This odds ratio corresponds to the lower bound of a one-sided confidence interval for the event rate given in ProTwin*Kids* Trial[25]. To reach a power of at least 80% for a Cochran-Mantel-Haenszel test for the primary outcome, we have to evaluate at least 500 patients,

250 in the pessary group and 250 in the control group. To account for a dropout rate of 25%, overall n=672 pregnant women will be recruited.

The reported response rate of the ProTwin*Kids*[25] study served as a basis for the assumed dropout rate of 25 % for the primary outcome measure >children`s survival without neurodevelopmental disability at the age of 3<. For both studies, the follow-up time was 3 years.

Recruitment

The obstetrics departments of the participating centres will counsel women with a twin pregnancy and refer them for the regular preventive ultrasound examination from 16 weeks onwards or due to a suspected cervical incompetence.

The obstetrical specialist will confirm that the patient fulfils the inclusion criteria and the study will be proposed. The patients will be informed about the intended therapeutic effect and possible side effects. The patient will be given an information sheet and the requisite time to reflect on participation. In case of participation and after having obtained their informed consent, they will be randomised in two groups either control group with usual management or pessary group with immediate placement of the cervical pessary. We expect patient recruitment to take approximately 2 years (Figure 1).

Randomization and masking

After providing written informed consent all women will be randomly allocated to the cervical pessary group or the control-group in a 1:1 ratio. The randomization sequence is computer generated with variable block sizes using a web-based e-CRF (Online-Software Castor[26] is a fully GCP compliant system) stratified for gestation groups and centers. The allocation code will be disclosed after the patient´s initials will be confirmed. The investigators or the trial coordinator will not have access to the randomization sequence. Neonatologists and pediatricians assessing the children will not be aware of the allocated treatment. The study is open label since masking the intervention is not possible.

Methods: Data collection, management and analysis

Data collection

The primary outcome measure “children´s survival without neurodevelopmental disability at the age of 3 years” will be collected by the standardized screening questionnaire Ages & Stages Questionnaire ASQ-3 (at 36 month of corrected age). The ASQ-3 is a parental questionnaire which is frequently used for screening developmental delay in problem solving, communication, fine- and gross motor skills and personal-social behaviour of preschool aged children[27,28]. Additionally the results of a regular preventive examination at paediatrician for children aged 34-36 month (in Germany *Vorsorgeuntersuchung U7a* or equivalent examination in Greece) are recorded.

All data for the secondary endpoints will be routinely collected during the course of the pregnancy and birth in the data management system of the caregiving hospital.

All investigators will be trained in pessary application. Quality protocols will be submitted according to the Clara-Angela Foundation requirements for pessary placement.

Data management:

Impetus Trial will be conducted according to standard operating procedures (SOP) of the Sponsor. These SOPs describe the processes during planning, conduct and evaluation as well as the quality management. It includes a predefined Data Management Plan (DMP), Data Validation Plan (DVP) and statistical analysis plan (SAP) including a description how to handle missing or implausible data. Source data verification will be performed in randomly selected centres (5%) as well as in randomly selected patients (5%) N=35

An electronic archiving of all reports and documents will be done for at least 10 years.

All data will be collected and processed in standardized electronic case report forms (eCRF) specially designed for Impetus Trial (=eCRF-Impetus). A feasibility assessment of the eCRF-Impetus will be done before start of the RCT, regular electronic checks for completeness and plausibility will be carried out. All AE reporting is done in eCRF. Castor EDC[26] is the Impetus eCRF software/database which complies with all applicable laws and regulations (Good Clinical Practice,

21 CFR Part 11, EU Annex 11; General Data Protection Regulation, HIPAA (US) ISO 9001 and ISO 27001). Castor is a validated system and approved by external auditors.

Safety: All SAR/SAE/AE will be reported to Sponsor who will notify *Landesärztekammer Hessen Ethikkommission*, all SAR/SAE (life-threatening or resulting in death) within 24 hours, all not life-threatening AE within 15 days, all AE will be recorded.

Statistics

The primary statistical aim is to compare the primary combined outcome “children`s long-term survival without neurodevelopmental disability at 3 years follow up” with a two-sided Cochran-Mantel-Haenszel-Test and a significance level of alpha=0.05 using 3 strata according to week of gestation. The primary outcome refers to a combined event in any of the twin and will be analyzed for all pregnancies with available primary endpoint. The stratified study design is accounted by this stratified test according to the gestation groups. Primary efficacy endpoint will be analyzed for all pregnancies with available primary endpoint.

No imputation method is planned. Nevertheless, to account for attrition bias, group allocations in this patient cohort with available primary endpoint will base on an intention to treat basis and with a per protocol allocation as sensitivity analysis.

The main statistical evaluation will be performed at two time points. (1) The complete data set for the secondary endpoints will be available after the last women enrolled in this study has delivered her twins, so the analysis of these outcome parameter will be done right after this event. (2) The primary outcome will be evaluated 3 years after the last woman enrolled in this study has delivered her twins. A descriptive analysis by preterm birth will be carried out calculating means and medians for quantitative variables and proportions with 95% confidence intervals for categorical variables. In general, statistical comparisons with the pessary arm and the control arms or other group comparisons for primary and secondary outcomes will be performed with stratified tests as well as comparisons in the gestation subgroups. Events will be analyzed for each twin and for single children assuming appropriate random effect regression models. Further subgroup analyses

regarding the cervical length will be performed (e.g. CL 15 to 25mm and below 15mm). All tests will be two-sided using a significance level of alpha=0.05.

The secondary outcomes comprise preterm birth rates, need for hospitalization before birth, maternal adverse events, pessary intolerance vaginal infections and fetal / neonatal death as well as neonatal morbidity will be analysed with Cochran-Mantel-Haenszel Tests and Chi-Square Tests; time to birth will be analysed with cox regression. For the secondary outcomes birthweight, days of hospitalisation (neonates) van Elteren Tests and Wilcoxon-Mann-Whitney Tests will be used.

For the primary endpoint, we expect to have a dropout rate of up to 25% due to the long follow-up time (3 years) of the study based on ProTwin*Kids*[25]; but we do not expect to have lost data for the secondary endpoints because for these parameters the study has a short follow-up time till time to birth only.

Interim analysis

After birth of 300 twins the key safety parameters • rate of preterm birth ≤ 32WoG • death before discharge • rate of SAR/SAE • maternal death will be assessed by a one-sided test with alpha=2,5%. The trial will be terminated as negative if a disadvantage for the pessary-treatment can be found in one of these tests. To guarantee a high safety level the significance level is chosen more conservatively than in a Bonferroni correction.

Discussion

Cervical pessary treatment is a non-invasive, well-tolerated and cost-effective treatment option[17] which could be easily implemented in daily practice. But to establish evidence based therapeutic guidelines on secondary prevention of sPTB concerning the use of cervical pessaries the up to now existing database is not sufficient. Concerning the short-term children´s outcome a significant positive effect of cervical pessary treatment in twin pregnancies is described in 2 RCT´s [17,18] (N=267) but in the RCT of Nicolaides et al.[19] (N=214) no significant effect was reported.

Up to now only the ProTwin*Kids* Trial[25] (N children: 157 pessary group/ 111 control group) evaluated the long-term children´s outcome concerning cervical pessary treatment for the prevention of sPTB. In clinical registries, no RCT´s were published covering this important aspect; so the data of the Impetus Trial (N children=1000) are clearly needed. Concerning the pessary effect on sPTB and maternal outcome the data of more than 650 multiple gestations will help to establish the role of cervical pessaries and more than 1000 children will clarify the short (>1350 neonates) and long term (min. 1000 children 3 years corrected age) effect of a pessary treatment in twin pregnancies with a short cervix at three stages of the twin pregnancy (early 16-20 WoG; middle 20-24 WoG and late 24-28 WoG).

The results of the Impetus trial are needed to establish evidence based therapeutic guidelines for the prevention of PTB in twin pregnancies with shortened cervix and investigate the efficacy of pessary placement as soon as cervical shortening occurs by recruiting patients in three groups (see above; early, middle and late placement) after serial measurements of cervical length through transvaginal ultrasound. This RCT is a part of the first worldwide prospective meta-analysis in twin pregnancies called “the prospective meta-analyses of pessary trials” (PROMPT). This project is in line with the requirements of the Global Obstetrics Network[20] (GONet) summarizing registered RCTs in twin pregnancies all using CORE[3] outcome parameters.

Abbreviations

PTB: Preterm Birth; RCT: Randomized Controlled Trial; WoG: Week of Gestation; CL: Cervical length; US: ultrasonographic scan; ASQ-3: Ages and Stages Questionnaire-3 (36 month), eCRF: electronic Case Report Form; EC: Ethics Committee; SAR/SAE: Serious Adverse Reaction/ Serious Adverse Event, AE: Adverse Event

Ethics approval and consent to participate

The sponsor, participating centers and investigators ensure that this study will be conducted in accordance with the protocol, the principles of the Declaration of Helsinki, ICH Guidelines for Good Clinical Practice and in full conformity with relevant regulations as well as applicable national laws and in accordance with regulations and guidelines applicable to clinical trials relating to medical devices. The protocol, informed consent form, participant information sheet and any applicable documents were submitted to the reference Ethics Committee (*Ethik-Kommission der Landesärztekammer Hessen*, Frankfut/M, Germany) (EC) and written approval has been obtained (Reference number FF 34/2017). All substantial amendments to the originally approved documents will also be sent to the respective authorities for approval. All participating centers will file their own EC approval. Ethic approvals of the participating cites in Greece are not yet available as the Impetus trial is not yet recruiting. Per study site the study will not begin until the approval of the EC and their director's consent will be obtained.

Consent for publication

Provided.

Availability of data and material

All data will be recorded in an eCRF; the database is located on a website so it can be accessed worldwide by the participating centres. Every centre will receive a password and a username in order to access the database for recruitment, randomization and documentation of patient data. Hereby, a personal identification number will be assigned for every patient. Patient names will not appear in the databases. Every participating centre will have its own randomisation list.

All data collected and prepared in the context of the study shall be the property of the Sponsor, provided that participating center shall remain the owner of its source data.

Competing interests

The authors declare that they have no competing interests

Funding

We applied for a governmental fund at *Deutsche Forschungsgesellschaft* (DFG) in August 2017. An approval for the monetary funding is pending. The DFG is the central self-governing research funding organisation in Germany, so no competing interests are to be expected.

Authors' contributions

IK from Frankfurt/M conceived the study and participated in its design and coordination. EH from Frankfurt compiled the statistics and power analysis. All authors will participate in the acquisition of data. All authors read and approved the final manuscript. BWM will coordinate the data monitoring committee.

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We thank Prof. Dr. Ben Willem Mol (University of Adelaide, Australia), Prof. Dr. Dr. Birgit Arabin (Philipps-University of Marburg and Clara Angela Foundation, Germany) and Prof. Dr. Zarko Alfirevic (University of Liverpool, UK) for reviewing the trial protocol. We acknowledge the contribution of the Clara-Angela Foundation to support international collaboration.

Study status

The study is not yet recruiting.

Related articles

No publications have been submitted or published so far.

Dissemination policy

In accord with the participating centres the publication of the results is planned for the impact of Cervical Pessary Treatment for Prevention of Preterm Birth in Twin Pregnancies with Cervical Shortening on the prevention of preterm birth and the short-term outcome of the children (secondary endpoints) and after availability of the data of the children`s long-term survival without neurodevelopmental disability (primary endpoint) these will be published as well.

Sponsor Information

Bürgerhospital und Clementine Kinderhospital gGmbH, Frankfurt/M, Germany, CEO Wolfgang Heyl, Nibelungenallee 37-41, 60318 Frankfurt am Main, Germany, Tel: +49 69 1500 0

The initiating study center assumes the role of the sponsor and provides the study coordinator and principal investigator, no competing interests are to be expected. The sponsor is not associated in any possible way with the intervention used for this study.

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