

**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***

Code: IMPETUS-Trial

Version 1.2 (January 2018)

Summary

Description: Clinical Trial with a sanitary device in its authorized using conditions.

Title: **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

Sponsor: Bürgerhospital und Clementine Kinderhospital gGmbH, Frankfurt/M., Germany

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Sanitary device: The Arabin cervical pessary, which is CE-certified for preventing SPB (CE 0482 / EN ISO 13485: 2012 + AC:2012 annex III of the council directive 93/42 EEC).

Main objective: To assess the impact of placing a cervical pessary in twin pregnancies with cervical shortening on children`s survival without neurodevelopmental disability at the age of 3.

Study design: Prospective Open-label Multicentre International Collaborative Randomized Controlled Trial, in parallel groups, based on intention to treat comparing the placement of a cervical pessary with usual management in cases of twin pregnancies with cervical shortening

Main outcome: Children`s survival without neurodevelopmental disability at the age of 3 years.

Study population: Women attending the reference hospital due to a dichorionic twin pregnancy with cervical shortening \leq 25th percentile and fulfil the inclusion criteria the study will be proposed. The patients will be informed of the intended therapeutic effect and possible side effects. If they agree and after obtaining their informed consent, they will be randomised according to the respective gestational week to either usual management (=control group) or cervical pessary placement up to 37+0 weeks (= pessary group). According to the gestational week and when the cervical shortening lies under the 25th percentile the patients are randomized to the following subgroups: gestational age in weeks 16-20, gestational age in weeks 20-24 and gestational age in weeks 24-28.

Sample size:

A stratified design, which divides the sample among 3 strata according to week of gestation, is analysed using the two-sided, Chochran-Mantel-Haenzel test with a significance level of $\alpha=5\%$. Sample sizes, summed across all strata, of 250 in group 1 (pessary group) and 250 group 2 (control-group), overall 500, achieve 80% power to prove significant difference when the odds ratio is actually 2,29 corresponding to the lower limit of a one-sided 90% confidence interval of the results in van't Hooft (ProTwin Trial)¹².

To account for a drop out rate of 25%, overall n=672 pregnant women will be recruited.

Study calendar:

Starting recruitment: July 1st, 2018

Finishing recruitment and follow-up: Dec 31st, 2023

Final report: July 2024.

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1. General information

1.1. Title, protocol identifying number and date.

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

Code: The Impetus-Trial

Version and date: version 1.2 (January 2018)

1.2. Name and address of the Sponsor.

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2. Rationale

2.1. Justification of the relevance of the trial.

Preterm birth (PTB) is a major contributing factor to perinatal morbidity and mortality. Prematurity requires intensive medical care for the neonate and is associated with an increased risk of mortality, disability, and developmental disorders later in life.^{1,2}

Women with a twin pregnancy are at increased risk of preterm delivery. In the Netherlands, approximately 50% of women with a multiple pregnancy deliver before 37 weeks' gestation, of whom 9% deliver before 32 weeks.³ Also for the USA the rate of preterm birth was as high as 56.6% in twins and the preterm delivery rate before 32 weeks was 11.3%.⁴

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 \leq 25 mm.⁵ This measurement has become the method of choice for screening asymptomatic pregnant women at risk for preterm birth <24 weeks of gestation both in twin and singleton pregnancies.⁶

A cervical pessary to support the cervix in pregnant women with cervical insufficiency was introduced in 1960. A cervical pessary is a silicone ring with a smaller diameter to be fitted around the cervix and a larger diameter to fix the device against the pelvic floor. This effectively rotates the cervix toward the posterior vaginal wall and corrects the cervical angle.⁷

In a prospective randomised trial the "ProTwin Trial"⁸ 813 women with twin pregnancies at a gestational age of 16 weeks to 20 weeks were randomised to either

pessary treatment or expectant management. Subgroup analysis of women with a shortened cervix below the 25 percentile (=38 mm) showed for the pessary group a significant 6-fold decrease in perinatal mortality and a reduction of severe morbidity. This demonstrates that an early screening followed by an early intervention is essential for patients at-risk. A secondary analysis “*per protocol*” of the ProTwinTrial revealed that the success of pessary treatment was mostly dependent on the correct placement and the duration of the therapy ⁹.

A further prospective-randomised trial by Goya et. al ¹⁰ also proved a significant reduction of the preterm delivery rate in twin pregnancies with cervical shortening (<25 mm, 20-24 weeks of gestation) after placement of a pessary compared to expectant management; the reduction in mortality was less pronounced than in the ProTwin Trial. A new case-control-trial by Fox et al. ¹¹ showed a decrease in early preterm birth before 32 weeks of gestation (4.8% vs. 28.6%, P=.05), a considerable prolongation of pregnancy (65.2 d. vs. 52.1 d, P=.025) and a reduced neonatal morbidity (9.5% vs. 34.9%, P=.04) in twin pregnancies after pessary therapy.

A secondary analysis of the ProTwin Trial indicated a higher survival rate without neurodevelopmental disability in the long-term outcome 3 years after pessary treatment (92.4 vs. 73.8%, p=0.006) compared to expectant management ¹².

A prospective, randomised controlled trial by Nikolaides ¹³ and a cohort study by Monfrance ¹⁴ in twin pregnancies with short cervix showed no significant effect of the pessary therapy compared to expectant management.

Up to now there is just one Cochrane review available concerning pessary therapy and the authors concluded that in spite of the positive effects seen that more trials should be conducted ¹⁵.

2.2. Description of the study population.

Women attending the reference hospital due to cervical shortening in twin pregnancies and fulfil the entry criteria (dichorionic twin pregnancy with cervical shortening \leq 25th percentile and do not fulfil the exclusion criteria), the study will be proposed. The patients will be informed of the intended therapeutic effect and possible side effects. If they agree and after obtaining their informed consent, they will be randomised according to the respective gestational week to either usual management (=control group) or cervical pessary placement up to 37 weeks (=pessary group). According to the gestational week and when the cervical shortening is under the 25th percentile the patients will be randomized to the following subgroups: gestational age in weeks 16-20, gestational age in weeks 20-24 and gestational age in weeks 24-28.

Specifically, the 25th centile of cervical length is defined at 32 mm, 30 mm and 28 mm for the 16+0 – 19+6, 20+0 – 23+6 and 24+0 – 28+0 weeks of gestation respectively.

2.3. Name and description of the device under investigation.

The Arabin cervical pessary, which is CE-certified for preventing SPB (CE 0482 / EN ISO 13485: 2012 + AC:2012 annex III of the council directive 93/42 EEC).

See annex I.

2.4. Statement that testing will be performed according to protocol, GCP and applicable legal requirements.

The Clinical Trial will be conducted following the protocol, the GCP, and all legal requirements.

3. Objective

This study aims to investigate the benefit of placing a cervical pessary in comparison to the expectant standard management in dichorionic twin pregnancies with cervical shortening \leq 25 percentile in terms of long-term survival without neurodevelopmental disability of the children.

Hereby, a standardized validated test called 'Ages and Stages 3rd edition' should evaluate the children's neurodevelopment at the age of 3 years. The test can be conducted by the parents and takes approximately 12 minutes. The questionnaires will be provided by the sponsor.

4. Design

4.1. Specific description of primary and secondary variables.

4.1.1. Primary outcome:

- Children`s survival without neurodevelopmental disability at the age of 3.

4.1.2. Secondary outcomes:

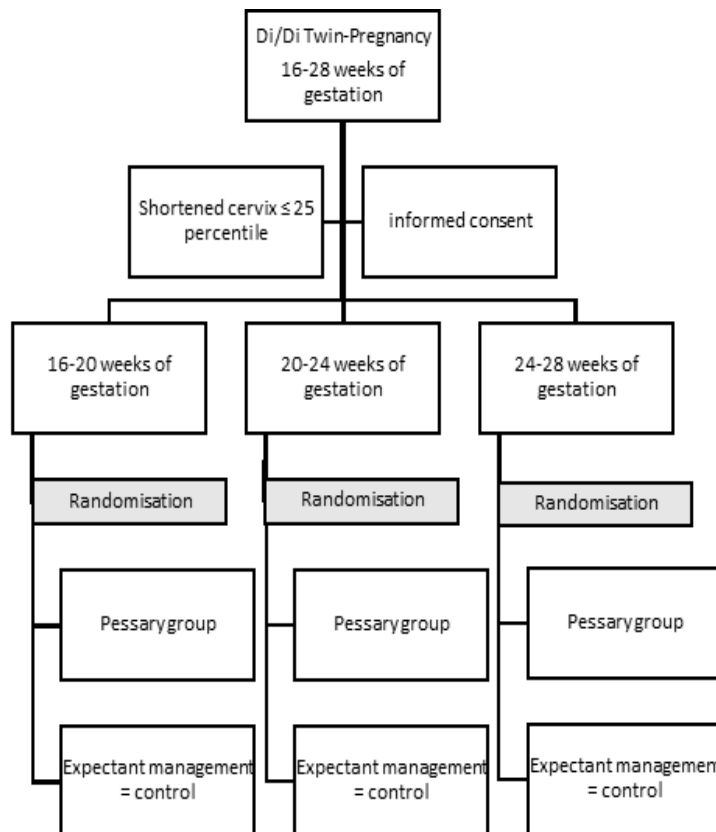
- Offspring
 - Time to birth
 - Preterm birth before 37 weeks: rate of delivery before 36+6 weeks
 - Preterm birth before 34 weeks: rate of delivery before 33+6 weeks
 - Preterm birth before 32 weeks: rate of delivery before 31+6 weeks
 - Preterm birth before 30 weeks: rate of delivery before 29+6 weeks
 - Preterm birth before 28 weeks: rate of delivery before 27+6 weeks
 - Birth weight: median weight (g) of the newborns at birth
 - Fetal or neonatal death: rate of intrauterine demise or neonatal death during the first 24 hours
 - Neonatal morbidity: rate of major adverse neonatal outcomes before discharge from the hospital
 - Intraventricular Haemorrhage (IVH): grades III-IV
 - Retinopathy of prematurity
 - Respiratory Distress Syndrome (RDS): grades II-IV,
 - Need for ventilation > 72 h
 - Necrotising enterocolitis
 - Proven or suspected sepsis, antibiotics (>5 days)
 - Need (Duration in days) for neonatal special care (NICU)
 - Harm from intervention
- Mother:
 - Maternal death
 - Significant maternal adverse events (rate):
 - Heavy bleeding: bleeding that requires a medical intervention
 - Cervical tear: cervical rupture due to the pessary placement
 - Uterine rupture: rupture of the uterus due to contractions or surgery
 - Physical or psychological intolerance to pessary: discomfort or pain due to the pessary that makes daily life uncomfortable (number of cases)
 - Rupture of membranes before 32 weeks: rate of–rupture of amniotic membranes before 31+6 weeks

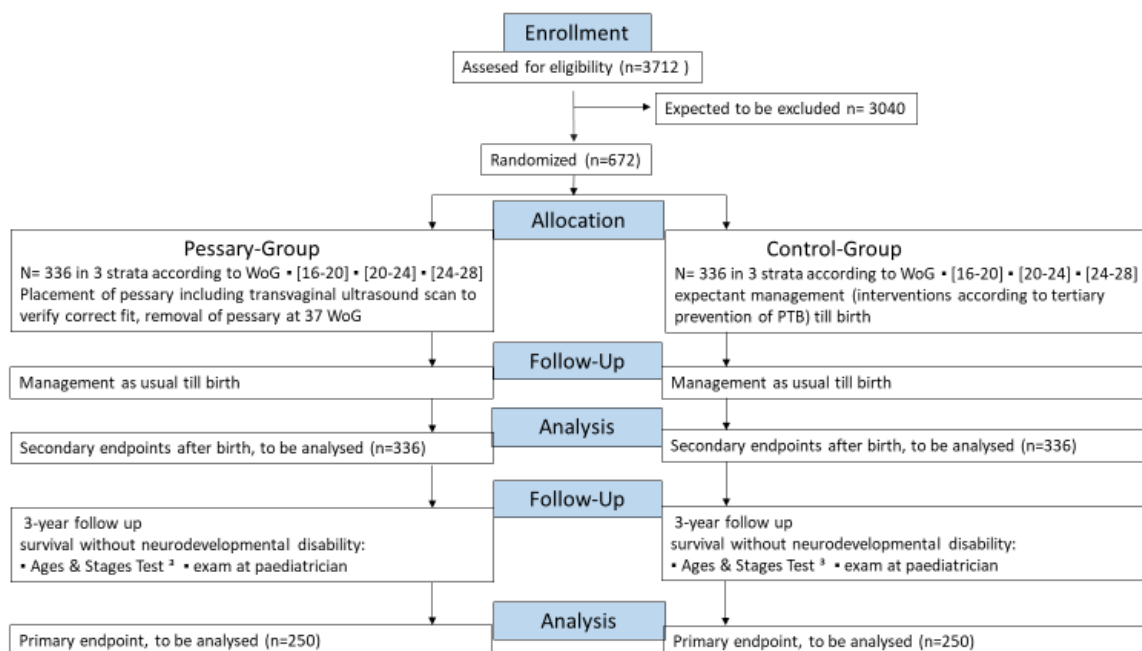
- Infection/inflammation
- Hospitalisation for threatened preterm labour before 32 weeks: requirement of hospitalisation due to preterm contractions that need medical treatment to try to stop them before 31+6 weeks (rate)
 - Mean hospital stay duration: number of days of admittance at the hospital
 - Use of tocolytic treatment: Type of tocolytic, days of treatment, dose

4.2. Description of the trial design.

Open Multicentre International Collaborative Randomized Controlled Trial, in parallel groups, based on intention-to-treat analysis comparing the placement of a prophylactic cervical pessary with usual management in twin pregnancies with shortened cervix ≤ 25 percentile

4.3. Flowchart.





4.4. Description of the medical device and the treatment regimen.

The cervical pessary is a vaginal device (silicone ring) that is used to treat pregnant women for preventing spontaneous preterm birth. This device can be easily placed around the uterine cervix without pain (see annex I).

If a woman with a dichorionic twin pregnancy at a gestational age of 16 weeks up to 28 weeks is diagnosed with a shortened cervix \leq 25 percentile during a preventive examination in pregnancy her vaginal pH-value is checked to preclude a vaginal infection. If her pH-value is $< 4,4$ she will be informed about the ongoing trial. If she is willing to participate and gives her informed consent, the woman will be randomized according to her respective gestational age to either pessary treatment group or expectant management group.

If the pregnant woman is assigned to the pessary group the pessary will be inserted directly. This procedure does not need anaesthesia and it does not need to be done in a surgery room. After the insertion of the pessary the correct fit of the pessary is verified by transvaginal ultrasound and in case it does not fit perfectly, it can easily be adjusted. The pessary will be removed at 37 weeks of gestation, or before if any unexpected event occurs (see 4.6).

After insertion of the pessary the obstetrical management during the pregnancy will be the same in both groups. Further surveillance of the pregnancy will not be influenced by the participation on the study.

4.5. Expected duration of subject's participation.

Study calendar:

Starting recruitment: July 1st, 2018

Finishing recruitment and follow-up: Dec 31st, 2023

Final report: July 2024.

4.6. Completion and interruption criteria of the study or the subjects.

The pessary will be removed at 37+0 weeks of pregnancy. The indications to remove them before this time will be: active bleeding stronger than usual period bleeding, persistent contractions after tocolysis and premature rupture of the membranes after 34 weeks.

After removing the pessary, the obstetrical management will be done as usual and will not be influenced by the study.

4.7. 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 PD Dr. Ioannis Kyvernitakis, Bürgerhospital Frankfurt/M. (Webmaster).

4.8. 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".

4.9. 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.

5. Selection and withdrawal of subjects

5.1. Inclusion criteria.

- Dichorionic diamnionic twin pregnancy with
- 16-28 weeks of gestation
- Minimal age of 18 years
- Informed consent signature

5.2. Exclusion criteria.

- Monochorionic twin pregnancy
- Major fetal abnormalities (requiring surgery or leading to infant death or severe handicap)
- Cerclage prior to randomisation
- Uterine malformation
- Placenta previa totalis
- Active vaginal bleeding at the moment of randomization
- Spontaneous rupture of membranes at the time of randomization
- Silicone allergy

- Current participation in other RCT
- Painful regular uterine contractions

5.3. Withdrawal criteria.

If a participant may voluntarily withdraw from treatment or if it is necessary to remove the pessary due to the conditions described before, the patients will be followed as usual until delivery (intention-to-treat analysis).

The death of one twin is not an exclusion criterion for the pessary placement.

The replacement of patients is not applicable in this trial.

5.4. Rescue treatment criteria.

If the cervical length decreases later on during the pregnancy, the management of the pregnancy in each centre will be the usual.

In case of secondary cervical shortening in the follow-up period pessary treatment may be offered as a rescue treatment up to 32+0 weeks of gestation.

Cervical cerclage or progesterone are generally not indicated in twin pregnancies.

6. Treatment of Subjects

6.1. Treatments to be administered.

The pessary will be inserted during a preventive examination in pregnancy in the examination room. This procedure does not need anaesthesia and it does not need to be done in a surgery room. After the insertion of the pessary the correct fit of the pessary is verified by transvaginal ultrasound and in case it does not fit perfectly, it can easily be adjusted. The pessary will be removed at 37+0 weeks of gestation, or before if any unexpected event occurs (see 4.6).

After insertion of the pessary the obstetrical management during the pregnancy will be the same in both groups. Further surveillance of the pregnancy will not be influenced by the participation on the study.

7. Efficacy assessment

7.1. Specification of efficacy parameters: Primary and secondary endpoints.

This study aims to investigate the benefit of placing a prophylactic cervical pessary in comparison to the usual management in twin pregnancies with cervical shortening ≤ 25 percentile in terms of long-term survival without neurodevelopmental disability of the children.

7.2. Methods and timing to assess records and analyze the efficacy parameters.

The patients will be assessed according to usual management in a twin pregnancy.

	Regular preventive exam	Regular preventive exam	Postnatal evaluation	3 years follow up (corrected age)
Study procedure	study inclusion			
Informed consent	x			

Randomisation	x			
Pessary placement	x			
Pessary removal		x at 37 WoG		
physical exams				
Abdominal US	x	x		
Vaginal US	x Cervical length ≤ 25 percentile			
pH-Value	pH < 4,4			
Neonatal Examination			x	
Ages and stages test				x
Exam at paediatrician				x

8. Assessment of Safety

8.1. Procedures to record and report adverse events.

If a serious and unexpected adverse effect occurs during pessary treatment, it will be notified to the study Sponsor. The Department of Obstetrics and Gynecology of the Sponsor will fill the side effects document to notify it to the *Landesärztekammer Hessen*.

The patient affected by the adverse effect will be followed more intensively during the first days and if nothing else occurs, she will return to the standard control.

8.2. Definitions.

Adverse Event (AE): Any untoward medical occurrence in a patient or clinical investigation participants administered a medicinal product, which does not necessarily have to have a causal relationship with this treatment (the study medication). An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the study medication/procedure, whether or not considered related to the study medication.

Adverse Reaction (AR): All untoward and unintended responses to a medicinal product related to any dose. The phrase "responses to a medicinal product" means that a causal relationship between a study medication and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the study medication / procedure qualify as adverse reactions.

Serious Adverse Event (SAE): A serious adverse event is any untoward medical occurrence that at any dose: Results in death; is life-threatening, NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe; Requires inpatient hospitalization or prolongation of existing hospitalization; Results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

Other important medical events: Other events that may not result in death, are not life threatening, or do not require hospitalization, may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning as defined in the bullet points above. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Serious Adverse Reaction (SAR): An adverse event (expected or unexpected) that is both serious and, in the opinion of the reporting investigator, believed with reasonable probability to be due to one of the study treatments, based on the information provided.

Suspected Unexpected Serious Adverse Reaction: A serious adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational product or summary of product characteristics for an approved product).

8.3. Procedures for immediate notification of serious or unexpected adverse events.

All AEs occurring during the study /or observed by the investigator or reported by the participant, whether or not attributed to study medication, will be recorded on the CRF. The following information will be recorded: description, date of onset and end date, severity, and assessment of relatedness to study medication, other suspect drug or device and action taken. Follow-up information should be provided as necessary.

AEs considered related to the sanitary device, as judged by a medically qualified investigator, will be followed until resolution or the event is considered stable. All related AEs that result in a participant's withdrawal from the study or are present at the end of the study, should be followed up until a satisfactory resolution occurs.

It will be left to the investigator's clinical judgment whether or not an AE is of sufficient severity to require the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must undergo an end of study assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

A medically qualified investigator will assess the relationship of AEs to the study medication.

All SAEs must be reported to the main investigator. He will perform an initial check of the report, request any additional information, and he will notify it to the Ethics Committee. All SAE information will be recorded. It may be appropriate that some SAEs do not require immediate reporting but this must be justified. Justification might be determined, for example, by admission to hospital, or prolongation of hospitalization, where this is to be expected in the underlying disease or condition.

All adverse events (AE) life-threatening or resulting in death will be notified within 24 hours. All AE that are not life-threatening will be notified within 15 days. The rest of AE will be recorded and analyzed at the end of the study.

9. Statistics

9.1. Description of statistical methods.

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

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 analysed 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, see also examples in the synopsis, will be two-sided using a significance level of $\alpha=0.05$.

For the primary endpoint we expect to have a drop out rate of up to 25% due to the long follow-up time (3 years) of the study; 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.

An interim analysis shall be conducted on key safety parameters after birth of 300 twins: the following safety endpoints will be assessed by a one-sided test with $\alpha=1\%$

- on level of the neonates: rate of preterm birth, time to birth, birth weight, death, neonatal morbidity, harm of intervention
- and on the maternal level: rate of hospitalisation for threatened preterm labour < 32 weeks, rate of PRoM <32 weeks, rate of infection / inflammation, rate of physical or psychological intolerance to pessary, rate of SAR/SAE, death.

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.

All analysis will be carried out with SPSS® version 19.0 or later (IBM Company SPSS Inc. Headquarters, Chicago, Illinois, USA) and R version 3.2.3 or later (R Foundation for Statistical Computing, Vienna, Austria).

Primary Outcome	Statistical Test
Children`s Long-Term Survival without Neuro-developmental Disability (3-Years-follow up)	Cochran-Mantel-Haenszel-Test, using 3 strata according to WoG
Secondary Outcome	Statistical Test
Birth before 34 Weeks of Gestation	Cochran-Mantel-Haenszel-Test, Chi-Quadrat Test
Time to Birth	Cox-Regression
Birthweight	van Elteren Test, Wilcoxon-Mann-Whitney Test
Fetal / Neonatal Death	Cochran-Mantel-Haenszel-Test, Chi-Quadrat Test
Neonatal Morbidity	Cochran-Mantel-Haenszel-Test, Chi-Quadrat Test
Need for Hospitalization (mother)	Cochran-Mantel-Haenszel-Test, Chi-Quadrat Test
Days of Hospitalization (mother)	van Elteren Test, Wilcoxon-Mann-Whitney Test
Maternal Adverse Events	Cochran-Mantel-Haenszel-Test, Chi-Quadrat Test
Pessary Intolerance	Cochran-Mantel-Haenszel-Test, Chi-Quadrat Test
Vaginal Infections	Cochran-Mantel-Haenszel-Test, Chi-Quadrat Test

9.2. Expected number of subjects to be included.

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 correspond to the lower bound of a one-sided confidence interval for the event rate given in van't Hooft (ProTwin Trial¹²). To reach a power of at least 80%, we have to evaluate at least 500 patients, 250 in the pessary group and 250 in the control group. To account for a drop out rate of 25%, overall n=672 pregnant women will be recruited.

9.3. Criteria for termination of the trial.

A non-justified case of maternal death (temporary stop until complete evaluation of the case by an external committee).

9.4. Selection of subjects to be included in each analysis.

The analysis will include all the subjects that have been randomised.

10. Direct Access to Data Source

Direct access will be granted to the authorized monitor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

11. Quality and Control Assurance

Main investigator and collaborators: In order to ensure the Quality of the data they will provide instructions and training to the sites involved in the trial; review the CRF data; and detail of any other steps taken to ensure quality of research.

The main investigator will sign the study protocol and the “investigator’s commitment; he will apply for the Ethics Committee and the Director’s approval; and he will review the final report of the study.

The collaborators will assess patient’s eligibility, they will inform the patients and ask for the informed consent; and they will be responsible of the CRF and obtaining and registering all data.

Monitor: he will perform regular monitoring according to ICH GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable and local regulatory requirements.

Serious Breaches: A serious breach is defined as “A breach of GCP or the trial protocol which is likely to effect to a significant degree: (a) the safety or physical or mental integrity of the subjects of the trial; or (b) the scientific value of the trial”. All serious breaches will be notified to the competent Regulatory Authority according to applicable legislation.

12. Ethical issues

The Sponsor, participating Centres and Investigator will ensure that this study is conducted in accordance with the Protocol, the principles of the Declaration of Helsinki (see annex III), ICH Guidelines for Good Clinical Practice and in full conformity with relevant regulations as well as applicable national laws, the German Law 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 will be submitted to an appropriate Ethics Committee (EC) and Regulatory Authority for written approval. All substantial amendments to the original approved documents will be also sent to an appropriate Ethics Committee (EC) and Regulatory Authority for written approval. The study will not begin until the approval of the EC and Director's consent.

13. Data Management and Registry File

Patient's participation in the study will be annotated into the medical history.

The main investigator will perform a list with the participant's names, ID numbers and codes. He also will have a file with all the information referring to the study.

All the data will be collected in a database that will be accessed worldwide.

The randomisation will be done on a computer basis. Once entering in the website, if the patient fulfils the inclusion criteria, the computer generated list will randomise the patient to "pessary" or "control" group.

The excluded patients will be also collected in the database.

Every participating centre will have its own randomisation list, and it will be accessible with a username and password.

The trial staff will ensure that the participants' anonymity is maintained. Only a participant ID number on the CRF and in the electronic database will identify the participants. All documents will be stored securely and only accessible by trial staff and authorized personnel. The study will comply with the Data Protection Legislation that requires data to be anonymized as soon as it is mandatory to do so.

13.1. Data ownership

Sponsor and participating Center have expressly agreed that any and 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 and may utilize such data as it deems appropriate without the approval, but with the reliable communication of Sponsor. Furthermore, Sponsor will always have access to the Study data, in terms of good faith and cooperation, in order to improve their own knowledge and information.

14. Funds and Insurance

According to German legislation and Ethical Committee decisions, it is not necessary to enter into an insurance contract in order to cover patients while using this medical device in a clinical trial. Insofar as it has been issued with the appropriate certificate of the State Medicines Agency to the concrete use of the medical device.

Nevertheless, it will be mandatory to enter into a hedging insurance by any other participating centre of this clinical trial, in the case that it is mandatory according to the laws of their country.

No funding is provided for the study.

15. Publication policy

The Sponsor takes the commitment of publishing the results of the study; despite they are good or bad.

Promoter and participating Centre agree that publications or presentations of any of the results from the study shall be in accordance with accepted scientific practice, academic standards and customs.

Authorship and other related publications questions shall be addressed in accordance with the principles of the 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals' and in accordance with the requirements of the respective medical journal.

Sponsor agrees to ensure co-authorship for clinical co-investigators on any proposed multicentre publication.

Sponsor and participating Centres agree that at first they will strive to make a joint publication. After such joint publication or one year after termination of the study the following shall be agreed:

As a general principle, the parties agree that prior to submission of a publication or any other dissemination of the results, including oral presentation, the Sponsor shall have the right to prior review and comment on the content of the material to be published or presented within sixty (60) days following the receipt of the publication or any other dissemination of the results, and Participating Centre ensures that it will take Promoter's comments into due consideration.

16. Legal Issues

Both the Promoter and the participating Centre will enter into a contract (Annex V) before they can start randomizing patients.

This contract will prevail in case of lack of agreement from any of the parts.

17. References

1. Hille ET, Weisglas-Kuperus N, van Goudoever JB, et al. Functional outcomes and participation in young adulthood for very preterm and very low birth weight infants: the Dutch Project on Preterm and Small for Gestational Age Infants at 19 years of age. *Pediatrics* 2007; 120: e587–95.
2. Mwaniki MK, Atieno M, Lawn JE, Newton CR. Long-term neurodevelopmental outcomes after intrauterine and neonatal insults: a systematic review. *Lancet* 2012; 379: 445–52.
3. Schaaf JM, Mol BW, Abu-Hanna A, Ravelli AC. Trends in preterm birth: singleton and multiple pregnancies in the Netherlands, 2000–2007. *BJOG* 2011; 118: 1196–204.

4. Martin JA, Hamilton BE, Osterman MJK, Curtin SC, Mathews TJ. National vital statistics reports. Births: final data for 2013. 2015.
5. To MS, Skentou CA, Royston P, Yu CK, Nicolaides KH. Prediction of patient-specific risk of early preterm delivery using maternal history and sonographic measurement of cervical length: a population-based prospective study. *Ultrasound Obstet Gynecol* 2006;27:362-7.
6. Conde-Agudelo A, Romero R, Hassan SS, Yeo L. Transvaginal sonographic cervical length for the prediction of spontaneous preterm birth in twin pregnancies: a systematic review and meta-analysis. *Am J Obstet Gynecol* 2010;203:128.e1-12.
7. Arabin B, Alfirevic Z. Cervical pessaries for prevention of spontaneous preterm birth: past, present and future. *Ultrasound Obstet Gynecol* 2013;42:390-9.
8. Liem S, Schuit E, Hegeman M, Bais J, de Boer K, Bloemenkamp K, et al. Cervical pessaries for prevention of preterm birth in women with a multiple pregnancy (ProTWIN): a multicentre, open-label randomised controlled trial. *Lancet*. 2013;382(9901):1341-9.
9. Liem SM, Schuit E, van Pampus MG, van Melick M, Monfrance M, Langenveld J, et al. Cervical pessaries to prevent preterm birth in women with a multiple pregnancy: a per-protocol analysis of a randomized clinical trial. *Acta Obstet Gynecol Scand*. 2016;95(4):444-51.
10. Goya M, de la Calle M, Pratcorona L, Merced C, Rodo C, Munoz B, et al. Cervical pessary to prevent preterm birth in women with twin gestation and sonographic short cervix: a multicenter randomized controlled trial (PECEP-Twins). *American Journal of Obstetrics and Gynecology*. 2016;214(2):145-52.
11. Fox NS, Gupta S, Lam-Rachlin J, Rebarber A, Klauser CK, Saltzman DH. Cervical Pessary and Vaginal Progesterone in Twin Pregnancies With a Short Cervix. *Obstetrics and Gynecology*. 2016;127(4):625-30.
12. Van 't Hooft J. Long-term effects of cervical pessary for preterm birth prevention in twin pregnancy with short cervix: a 3 years follow-up of the ProTwin trial. *AJOG*2016.
13. Nicolaides KH, Syngelaki A, Poon LC, de Paco Matallana C, Plasencia W, Molina FS, et al. Cervical pessary placement for prevention of preterm birth in unselected twin pregnancies: a randomized controlled trial. *Am J Obstet Gynecol*. 2016;214(1):3 e1-9.
14. Monfrance JM, Schuit E, Groenwold RH, Oudijk MA, de Graaf IM, Bax CJ, Bekedam DJ, Mol BW, Langenveld J. Pessary placement in the prevention of preterm birth in multiple pregnancies: a propensity score analysis. *Eur. J Obstet Gynecol*. 2016; 197:72-77.
15. Abdel-Aleem H, Shaaban OM, Abdel-Aleem MA. Cervical pessary for preventing preterm birth. *The Cochrane database of systematic reviews*. 2013(5):CD007873.

18. Annex

Annex I. Technical details of the device.

The Arabin cervical pessary

CE-certified for preventing spontaneous preterm birth (CE 0482 / EN ISO 13485: 2012 + AC:2012 annex III of the council directive 93/42 EEC).

This pessary is used to treat pregnant women with cervical incompetence in order to support the cervix and sacralise it towards the sacrum.

It may be indicated in pregnancies with a history of premature labour, multiple pregnancies or mothers who are exposed to physical strain (e.g. standing for a long time). It may also be indicated in pregnant women suffering from prolapse of the genital organs.

The cerclage pessary can easily be folded and inserted without pain.

In general, cerclage pessaries should have a height of 21-25 mm in singleton pregnancies and a height of 25-30 mm in multiple pregnancies or pregnant patients with complaints of prolapse. The width of the upper and lower diameter should be chosen depending on the individual constitution of the pregnant patient.

Cerclage pessaries can be ordered in a non-perforated or perforated version. The perforations facilitate discharge to pass.

Sizes and Models: Cerclage pessaries are classified according to

- The lower larger diameter (65 or 70 mm)
- The height (17, 21, 25, 30 mm)
- The upper smaller diameter (32 or 35 mm)

Dr. Arabin online shop. <http://www.dr-arabin.de/e/cerclage.html>