Validation of a Novel Reusable Vacuum Extractor

a Comparative Mannequin Study between
the Vela Vacuum Extractor and the Kiwi Omnicup

Iris Meijer
MSc Biomedical Engineering
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by

Iris Meijer
4595424

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TU Delft supervisor: Prof. Dr. J. Dankelman
Layco Medical Devices supervisor: D. Drexhage
LUMC supervisor: Dr. P. Ramler
TU Delft external supervisor: Dr. R. Oosting
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Acknowledgment

I would like to express my sincere gratitude to a number of people, for their guidance and support throughout the course of this project.

First and foremost, I would like to express my sincere appreciation to my TU Delft supervisor, Jenny Dankelman, for her guidance throughout the entirety of this project. I am truly grateful for the time she dedicated to providing feedback, answering questions, and offering suggestions. Secondly, I would like to thank my daily supervisor Dieuwertje, for always being open to questions, giving endless support and providing good jokes every day.

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This project would not have been possible without the contributions and support of each and every one of these individuals, and for that, I am truly grateful.

Iris Meijer
January 2023

Contents

1 Introduction

In this chapter, an introduction is given regarding this thesis document. A short background of this study is provided, as well as a rationale for this research. Furthermore, the contents of this document are briefly explained.

1.1 Background of Thesis

This thesis is part of a graduation for the degree Master of Science Biomedical Engineering at the Delft University of Technology. This thesis was conducted in collaboration with the company Layco Medical Devices. Layco is a medical devices development company. In 2020, Layco was founded out of the following problem: the manufacturing of medical equipment worldwide is concentrated in – and designed for – high-income countries. As a result, current medical equipment does not always meet the local context of low- and middle-income countries (LMIC) [1, 2]. The ambition of Layco is to make high quality medical devices for everyone, everywhere. Currently, Layco is developing the Vela^{TM}: a reusable vacuum extractor. The reusable Vela was designed out of a need for the (re)introduction of vacuum extraction in LMIC.

Vacuum extraction is a form of instrumental delivery, in which the fetus is assisted out of the birth canal. During a vacuum extraction, a vacuum cup is attached to the fetal head by means of suction to which traction force is applied in cooperation with uterine contractions to facilitate birth. Indications for the need for a vacuum extraction are maternal fatigue, a non-reassuring fetal heart rate, a prolonged second stage of labor or the necessity to shorten the second stage of labor [3]. When instrumental delivery is required, e.g. 5% of all deliveries in the United States, a vacuum extractor is the preferred instrument [4, 5]. Unfortunately, most current vacuum extractor do not meet the needs for LMIC, either because they are too expensive or disposable (increasing price per usage), complicated to use, or they do not fit the local context. [6].

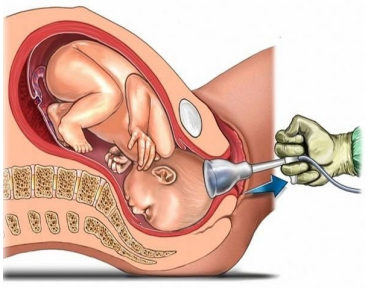


Figure 1.1: Illustration of a vacuum extraction, wherein a vacuum extractor is used to help facilitate the delivery of a fetus [7].

With the development of the Vela, Layco aims to provide a reusable vacuum extractor to make instrumental delivery achievable in LMIC, with the goal of facilitating deliveries and reducing maternal and neonatal mortality.

Regarding this thesis assignment, the scope was to design and conduct a mannequin study for the validation of the first prototype of the reusable Vela. Over a period of 9 months, this assignment was carried out by conducting a literature review, designing a study protocol and executing that study. Lastly, a scientific article was written, ready for publication. This thesis document contains all the mentioned steps of the graduation project.

1.2 Contents of Thesis

During the course of this thesis, several stages have passed. First of all, a journal article is presented in Chapter 2. This is the final result of this thesis and will therefore be presented first. This article contains the design of the study and includes the results and conclusions of the study. This article is to be published in a scientific journal.

Subsequently, the research protocol is presented in Chapter 3, which was submitted for ethical approval to the science committee and the non-WMO [1] committee of the Leiden University Medical Center (LUMC) and Nijmegen CWZ hospital. This research protocol contains, in detail the design of the study, how and where the study would be conducted, some ethical considerations and how the results were going to be analyzed.

1: *Dutch: Wet Medisch-wetenschappelijk Onderzoek.*

In Chapter 4, a study design rationale is presented, in which all the key choices will be (further) explained and substantiated, because space in the paper or protocol was limited.

Finally, Chapter 5 provides a reflection on this thesis, complementary to the discussion of the scientific paper. Here, choices are be reflected upon, alternatives are discussed and any setbacks from the study design are addressed.

To enable this study design, a literature review was conducted. This review sought relevant endpoints (measured parameters in scientific studies) for a validation study of a vacuum extractor. By identifying these parameters, endpoints for the mannequin study of this thesis could be established. This literature review 'An Insight into the Relevance of Endpoints in Vacuum Extractor Validation Studies' is presented in Appendix A.

Any additional documents are also presented as Appendices. Appendix B displays the questionnaire for the participants, Appendix C presents the informed consent form for participants and Appendix D depicts the approval by the non-WMO[1] committee of the LUMC.

Medical Journal Article 2

The following pages present the article that will be submitted for publication of the study 'Comparison between the Vela Vacuum Extractor and the Kiwi Omnicup: a randomised mannequin study' submitted to a scientific journal.

Comparison between the Vela™ Vacuum Extractor and the Kiwi® Omnicup

a randomized mannequin study

Author: I.E. Meijer
Supervisors: D. Drexhage & J. Dankelman
January 2023

Abstract*—*Background: **Vacuum extraction is a way to prevent unnecessary maternal deaths, by using a vacuum extractor to help deliver the baby in the second stage of labour. Vacuum extraction is still little-used in low- and middle-income countries (LMIC) compared to high income countries, due to the lack of sufficient devices on the market that fit the local context. For this purpose, a novel reusable and affordable vacuum extractor was designed. This study compares this device, the Vela™, with a commonly used vacuum extractor, the Kiwi Omnicup®, in terms of performance and user experience in a non-inferiority mannequin study.** ***Methods:*** **Obstetricians and residents from LUMC and CWZ hospitals performed a vacuum extraction on a birthing mannequin using both devices. During simulated "traction windows" of 25 seconds, the participant was allowed to pull. The primary endpoint was the traction window in which successful vacuum extraction occurred. Secondary endpoints were the total number of pop-offs of the cup, the exact success time within the successful traction window, the pumping time before the successful traction window, the satisfaction rate and the comparison between the two devices on placement, pumping and pulling. Finally, the participants were asked for their opinions about the Vela in an open-ended question.** ***Results:*** **A total of 47 participants were included in this study, of which three never achieved success with the Vela. For the primary endpoint, the Vela was non-inferior to the Kiwi in both LUMC and CWZ. Furthermore, no significant differences were found between the Vela and the Kiwi regarding any of the secondary endpoints, with exception of the satisfaction rate in the LUMC. This was significantly lower for the Vela. Themes raised by participants concerned the stiffness of the Vela tube, the comfort of the Vela during usage and the need for familiarization with a new device.** ***Conclusions:*** **The results of this study indicate that the Vela is non-inferior to the Kiwi Omnicup when used by clinicians who had success with both devices, however there is room for improvement regarding satisfaction of the Vela. More familiarization is needed and the tube of the Vela should be reduced in stiffness. With this initial validation, the Vela can be seen as a promising alternative for LMIC, and can be further optimized into a high-quality fully reusable vacuum extractor.**

I. Background

Improving maternal health remains a major challenge in global public health [1], and one of the targets in the Sustainable Development Goals is to reduce the maternal mortality ratio to less than 70 per 100.000 live births by 2030 [2]. In 2017, 810 women died every day from pregnancy- and childbirth-related causes [3]. The World Health Organization (WHO) found that 94% of all maternal deaths occur in low- and middle-income countries (LMIC), and were avoidable in most cases [4].

One way to reduce unnecessary maternal deaths is to obviate obstructed labour. Obstructed labour is one of the larger causes of maternal mortality in LMIC, and moreover accounts for 8% of all maternal deaths worldwide [5]. The ways to overcome obstructed labour are by either making use of a caesarean section or an instrumental vaginal birth (e.g. vacuum extraction).

A vacuum extraction is an evidence-based method of an instrumental vaginal birth used to help deliver the baby when labor is obstructed, prolonged, or when there are signs of foetal distress [6]. During this procedure, a vacuum extractor is placed on the baby's head and a negative pressure is created, after which the baby is born via traction. Vacuum assisted deliveries are widely performed in high-income countries (HIC) [7] [8]. However, vacuum extraction rates in LMIC have been significantly low, compared to HIC [9] [10]. In LMIC, the more common course of action is to perform a caesarean section, which is a lifesaving intervention, but has a substantially longer recovery time, costs more money and puts the mother at a higher risk of complications, such as infections or uterine rupture in a next pregnancy [11]. Therefore, the WHO encourages that unnecessary caesarean sections be avoided, and that alternatives for caesarean section become available in LMIC [12] [13]. One way to do this is by reintroducing vacuum extraction in LMIC [14].

A reason for the deficit of vacuum extractions in LMIC is that current vacuum extractors do not fit the local context in terms of affordability and accessibility. They are either too expensive, such as electrical vacuum extractors, have a complex design, or need proper training before correct implementation. The vacuum extractors that are user-friendly, such as the Kiwi® Omnicup, are not reusable, which also poses challenges in terms of affordability. As a result, current vacuum extractors do not meet the need for LMIC [15].

The novel Vela™ (Layco Medical Devices, Amsterdam) is a vacuum extractor that is reusable, affordable and intuitive. The current prototype of the Vela consists of a suction cup, which is connected via a tube to a vacuum hand pump. A pressure meter

is also integrated into the design, which indicates the required pressure on the foetal head. All the individual parts can be disconnected, which allows for proper cleaning of the Vela. Furthermore, because of its expected low-cost and sustainable nature, even HIC could benefit from the Vela.

Before deployment, proper functioning of the Vela needs to be carefully validated. The best way to do this is to compare it against the gold standard of vacuum extraction, the Kiwi Omnicup (Clinical Innovations Inc., Murray, UT, USA). In this study, the functioning of the Vela will be examined through a comparison trial between the Vela and the Kiwi Omnicup. Both vacuum extractors will be assessed on efficacy and user experience. The study will look for potential non-inferiority of the Vela compared to the Kiwi, with the hypothesis that the Vela is non-inferior to the Kiwi. As the Vela is still a prototype, the study will be carried out on mannequins.

II. Methods

Ethical approval for this study was granted by the ethics committees of the Leiden University Medical Center (LUMC), Canisius Wilhelmina Ziekenhuis (CWZ) Nijmegen and Delft University of Technology in September 2022. Participants were recruited on a voluntary basis in the LUMC and CWZ and were asked to complete a vacuum extraction on a mannequin with both the Vela and the Kiwi Omnicup. The inclusion criteria were that the participants were obstetricians or residents in obstetrics and were authorized to perform a vacuum extraction. An informed consent form was signed by the participant. Prior to the start of the study, oral instructions were given regarding the use of the vacuum extractor devices in terms of holding, pumping and establishing the correct pressure. Each participant was handed the Vela and the Kiwi Omnicup. Participants were offered a few minutes to familiarize themselves with the vacuum extractors and the mannequin. Participants had no prior knowledge of the Vela and during the vacuum extraction, only the participant and researchers were present in the room, ensuring no external influence. In total, five Vela's and five Kiwi's were used.

The study had a randomized design. Each participant performed one vacuum extraction with the Vela and one with the Kiwi Omnicup. The order of use of each device was determined using randomization. The vacuum extractions were performed on the Lucy and Lucy's Mum Instrumental Delivery Birth Simulator (Model Med, Victoria, Australia). Before each vacuum extraction, the Lucy mannequin was lubricated with water-based lubricant (Aquasonic). Lucy's head was placed in the mannequin each time positioned at the same position in occiput anterior by a researcher. The participant then placed the cup of the vacuum extractor on the head of Lucy and created a negative pressure by pumping.

The participant was told to perform a vacuum extraction with both devices until successful extraction. A successful vacuum extraction meant that the head of the mannequin baby was extracted during a "traction window". A traction window was simulated as 25 seconds, during which the participant was allowed to pull with the vacuum extractor. This traction window was started by the researcher. If there was no successful extraction during these 25 seconds or a pop-off occurred, a period of rest lasting ten seconds was mandated, after which the next traction window commenced. In Figure 1, the timeline of a vacuum extraction with one device can be seen. To standardise the method, Lucy's head was not pushed along on the back of the mannequin by the researcher at any point during the vacuum extraction.

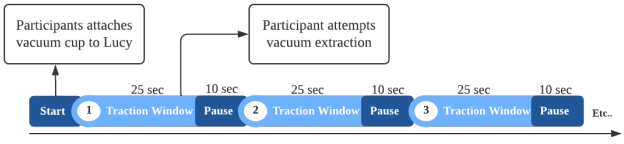


Fig. 1: Timeline for a vacuum extraction with one device.

The primary endpoint was the successful traction window, defined as the traction window in which successful vacuum extraction took place. Secondary endpoints were divided into performance and opinion endpoints. Performance endpoints were: the exact success time (measured in seconds) within the successful traction window, the pumping duration (measured in seconds) before the successful traction window and the total number of pop-offs of the cup. Opinion endpoints were satisfaction after each vacuum extraction on a 4-point Likert scale (1 = extremely satisfactory, 2 = satisfactory, 3 = unsatisfactory, 4 = extremely unsatisfactory) and the comparison made by the participant after both vacuum extractions on placement, pumping, pulling (Vela performs better (1), equal (2) or worse (3) than Kiwi). Ultimately, the participants were asked for their general opinion about the Vela and the difference compared to the Kiwi in an open question, which was audio-recorded.

The sample size was calculated using a sample size calculation for continuous outcomes in non-inferiority trials. Because there are no prior studies validating a vacuum extractor in a non-inferiority mannequin study, the standard deviation (SD) was determined by doing a pilot study with obstetricians from the LUMC. From five test-runs, a SD of 1.8 traction window was determined. Together with three obstetricians from the LUMC, a non-inferiority limit was set at 2 traction windows for the primary endpoint. With a significance level (α) of .05 and power ($1 - \beta$) of .9, it was calculated that a minimum of 9 participants were needed, to be 90% sure that the upper limit of a one-sided 95% confidence interval would be below the non-inferiority limit of 2.

In the statistical analysis, data was analysed using R software (version R 4.2.2). For the primary endpoint, the data was analyzed for non-inferiority using a one-sided paired samples t-test with the previously determined non-inferiority limit of 2 traction windows. The null hypothesis H_0 states that the Vela is inferior to the Kiwi and the alternative hypothesis H_a states the Vela is non-inferior to the Kiwi with the non-inferiority limit of 2 traction windows. If $p \leq .05$, the null-hypothesis is rejected and the alternative hypothesis that the Vela is non-inferior to the Kiwi is accepted for the primary endpoint [16].

Additionally, a standard paired t-test was conducted to look for significant difference on the primary endpoint.

For the secondary endpoints, success time, the pumping time, pop-offs and satisfaction, data was checked for significant difference of the results. This was done using a two-sided paired samples t-test, with H_0 stating that there is no difference between the Vela and the Kiwi. If $p \leq .05$, the null hypothesis is rejected, meaning there is a significant difference between the Vela and Kiwi for that endpoint. If $p > .05$, no significant differences were found between Vela and Kiwi for that particular endpoint. Additionally, the results of these four endpoints were interpreted by two obstetricians from the LUMC and CWZ. This was done by discussing the 95% confidence intervals of these endpoints.

Lastly, the secondary endpoint "comparison on placement, pumping and pulling" was analysed using descriptive statistics. Ultimately, the open-ended question was transcribed verbatim and coded inductively.

III. Results

In October and November 2022, a total of 47 obstetricians and residents from the LUMC (n = 31) and CWZ (n = 16) participated in this study. The data of the LUMC and the CWZ were analyzed separately, because of differences in the Lucy mannequin. There were three participants in the LUMC with missing data for the Vela, following drop-out on own initiative with the Vela. These participants were excluded from performance analysis, but included in the opinion analysis (see Figure 2).

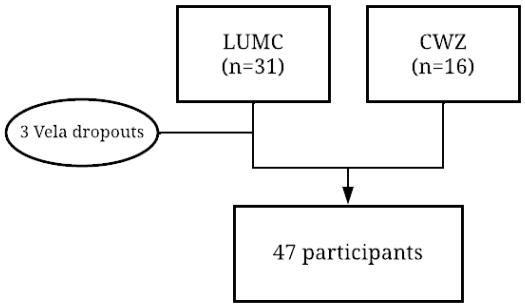


Fig. 2: Participants for LUMC and CWZ.

A. Primary Endpoint

For the primary endpoint, successful traction window, in LUMC, the mean number of traction windows needed for successful delivery with the Vela (2.5) was non-inferior to the mean traction windows needed with the Kiwi (2.5), with p = 0.003. Similarly, in CWZ the mean number of traction windows needed for successful delivery with the Vela (1.1) was non-inferior to the needed traction windows with the Kiwi (1.1) with $p < 0.001$. This means that for the primary endpoint, the Vela is non-inferior to the Kiwi Omnicup in both hospitals. In Figure 3, a graph of the occurrence of the successful traction windows for each hospital is shown. Additionally, in the paired t-test, no significant difference was found (p-value = 1.00) between the Vela and Kiwi on the primary endpoint.

B. Secondary Endpoints

For success time within the successful traction window in LUMC, means of 17.5 sec for the Vela and 17.2 sec for the Kiwi were found. In CWZ, means of 14.2 sec and 14.6 sec were found for the Vela and Kiwi, respectively. P-values of 0.757 and 0.667 were found in respectively LUMC and the CWZ, meaning no significant differences were found in LUMC and CWZ for this endpoint. In Figure 4, the difference Vela minus Kiwi per participant for success time is depicted.

For pumping time in LUMC, means of 8.2 sec and 8.9 sec for the Vela and Kiwi respectively were found. The data from three participants were missing for this endpoint. In CWZ, means of 6.4 sec for the Vela and 8.9 sec for the Kiwi were found. No significant differences were found for this endpoint in both LUMC (p = 0.357) and CWZ (p = 0.069). In Figure 5, the difference Vela minus Kiwi per participant for pumping time is depicted.

Regarding the pop-offs in LUMC, mean number of pop-offs of 1.5 and 1.4 for respectively the Vela and Kiwi were found. In CWZ, mean number of pop-offs of 0.1 and 0.0 were found for the Vela and Kiwi, respectively. No significant differences were found in both LUMC (p = 0.813) and CWZ (p = 0.333). Results can be seen in Figure 6.

For the satisfaction after each vacuum extraction (extremely satisfactory (1), satisfactory (2), unsatisfactory (3), extremely unsatisfactory (4)), means of 2.2 and 1.6 for respectively the Vela and Kiwi in LUMC were found. In CWZ, means of 1.8 and 1.6 for Vela and Kiwi were found. In LUMC, a significant difference was found for the satisfaction (p = 0.012). In CWZ, no significant difference was found (p = 0.188). In Figure 7, the results for this endpoint are depicted.

For the comparison between the Vela and Kiwi (Vela is better (1), equal (2) or worse (3) than Kiwi), means of 2.3, 2.0 and 2.3 for respectively the placement, pumping and pulling were found in the LUMC. In the CWZ, means of 2.2, 1.9 and 1.9 for respectively the placement, pumping and pulling were found. Figure 8 shows these results.
The results of the primary and secondary endpoints and corresponding p-values can be found in Table I.

During the clinicians' interpretations of the confidence intervals, at CWZ and LUMC all confidence intervals were considered acceptable for the discussed endpoints, except the satisfaction in the LUMC. The obstetricians indicated that the differences between the Vela and Kiwi shown in the accepted confidence intervals were small enough to suggest similarity between the devices.

TABLE I: Results for Primary and Secondary Endpoints
SD = Standard Deviation

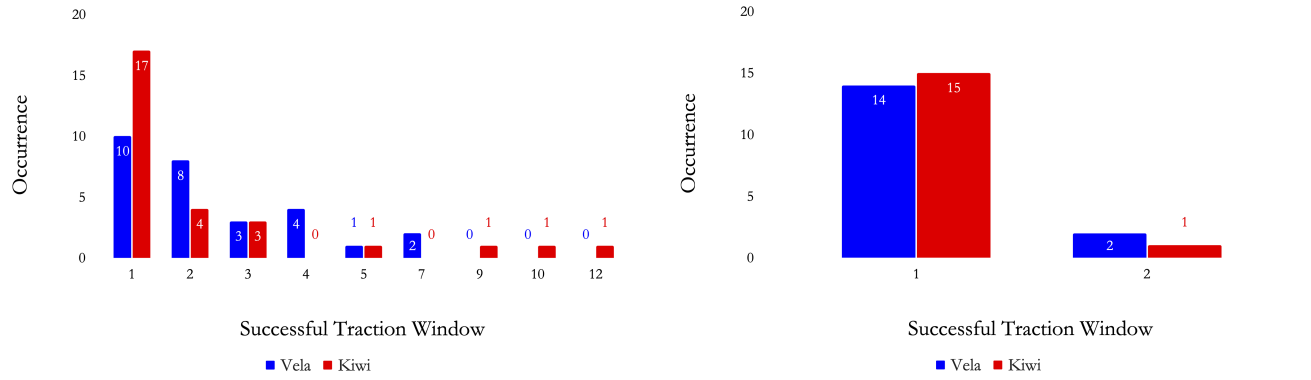
	LUMC			CWZ		
	Vela (**mean** ± SD)	Kiwi (**mean** ± SD)	p-value	Vela (**mean** ± SD)	Kiwi (**mean** ± SD)	p-value
	Primary Endpoint					
Successful Traction Window (#)	**2.5** ± 1.7	**2.5** ± 3.0	0.003	**1.1** ± 0.3	**1.1** ± 0.3	<0.001
	Secondary Endpoints					
Success Time (s)	**17.5** ± 5.6	**17.2** ± 6.0	0.757	**14.2** ± 5.8	**14.6** ± 5.1	0.667
Pumping Time (s)	**8.2** ± 4.7	**8.9** ± 6.9	0.357	**6.4** ± 3.2	**8.9** ± 5.0	0.069
Pop-offs (#)	**1.5** ± 1.8	**1.4** ± 2.6	0.813	**0.1** ± 0.3	**0.0** ± 0.0	0.333
Satisfaction (1-4)	**2.2** ± 0.9	**1.6** ± 0.7	0.012	**1.8** ± 0.4	**1.6** ± 0.5	0.188

C. Open Question

31 participants at LUMC and 16 participants at CWZ were included in the opinion analysis. The data from LUMC and CWZ have again been separated. The five most common themes raised by the participants were:

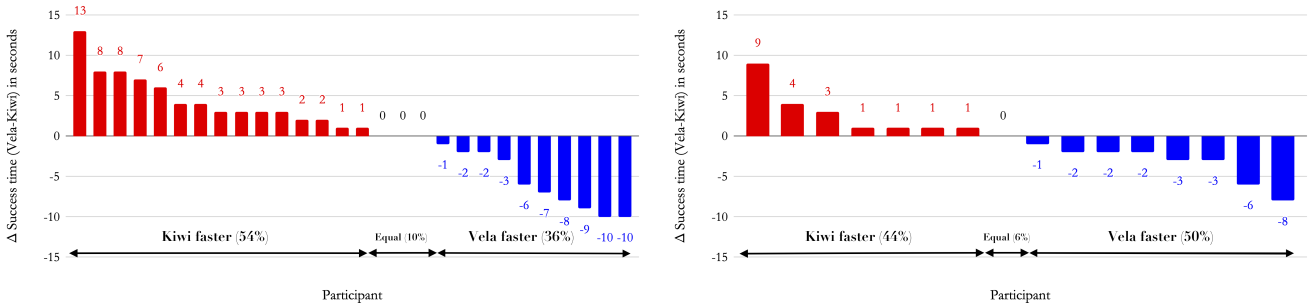
- *The tube of the Vela is too stiff* (LUMC 58%, CWZ 63%)
- *Problems with pumping of Vela* (LUMC 39%, CWZ 6%)
- *Satisfied about pumping with Vela* (LUMC 32%, CWZ 75%)
- *Vela is comfortable in use* (LUMC 58%, CWZ 44%)
- *Vela needs more familiarization* (LUMC 29%, CWZ 44%).

In Figure 9, an overview is given of all overarching themes that were addressed.



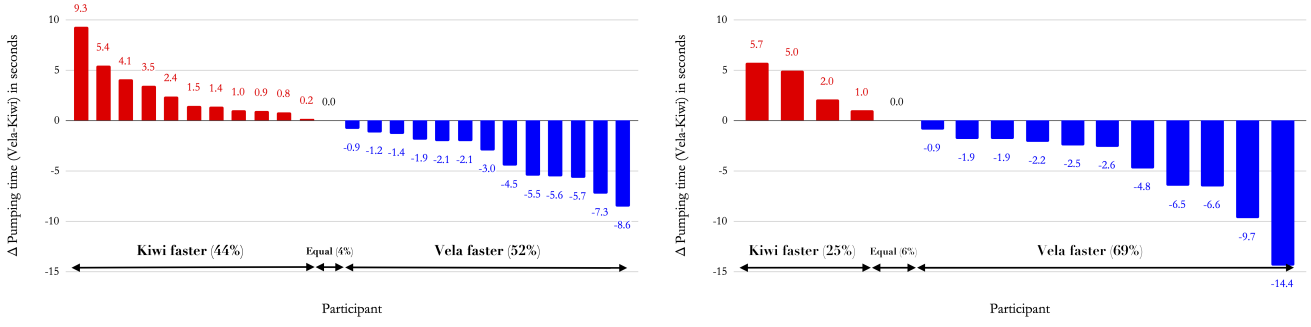
(a) LUMC (b) CWZ

Fig. 3: Occurrence (y-axis) of the number of traction windows (x-axis) needed for successful vacuum extraction, per hospital.



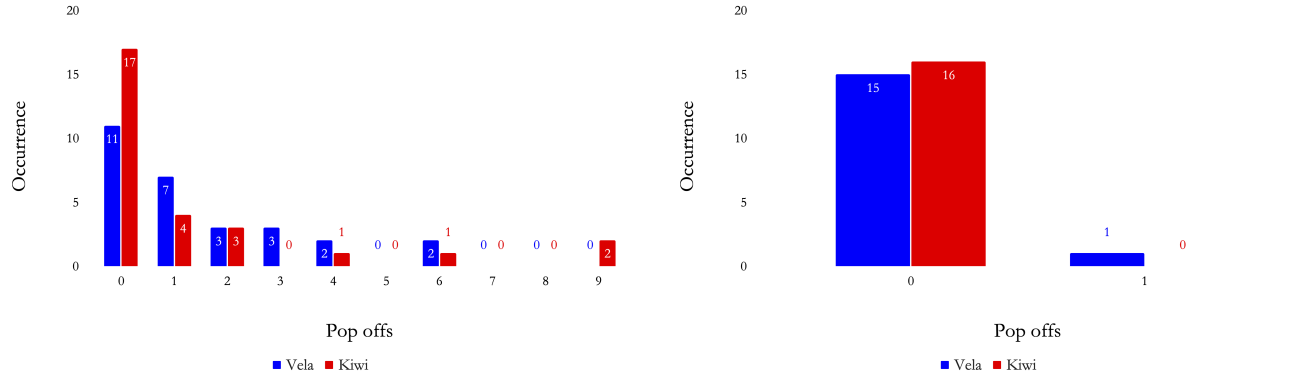
(a) LUMC (b) CWZ

Fig. 4: Difference in success time Vela minus Kiwi (y-axis) for each participant (x-axis), ranked from biggest positive difference to biggest negative difference.



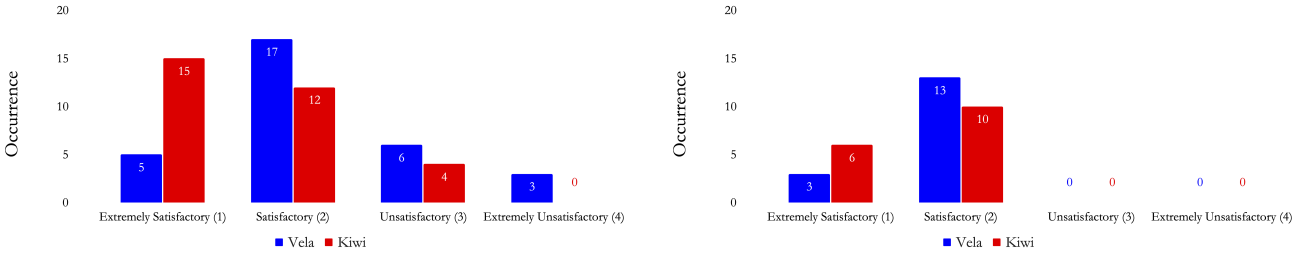
(a) LUMC (b) CWZ

Fig. 5: Difference in pumping time Vela minus Kiwi (y-axis) for each participant (x-axis), ranked from biggest positive difference to biggest negative difference.



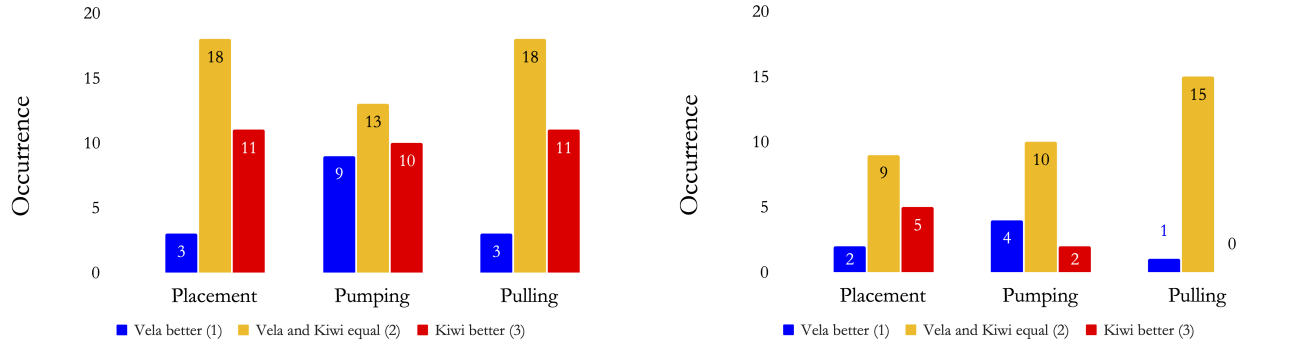
(a) LUMC (b) CWZ

Fig. 6: Occurrence (y-axis) of the total number of pop offs (x-axis).



(a) LUMC (b) CWZ

Fig. 7: Occurrence (y-axis) of the satisfaction rate (x-axis) after each successful vacuum extraction.



(a) LUMC (b) CWZ

Fig. 8: Occurrence (y-axis) of the comparison on placement pumping and pulling (x-axis).

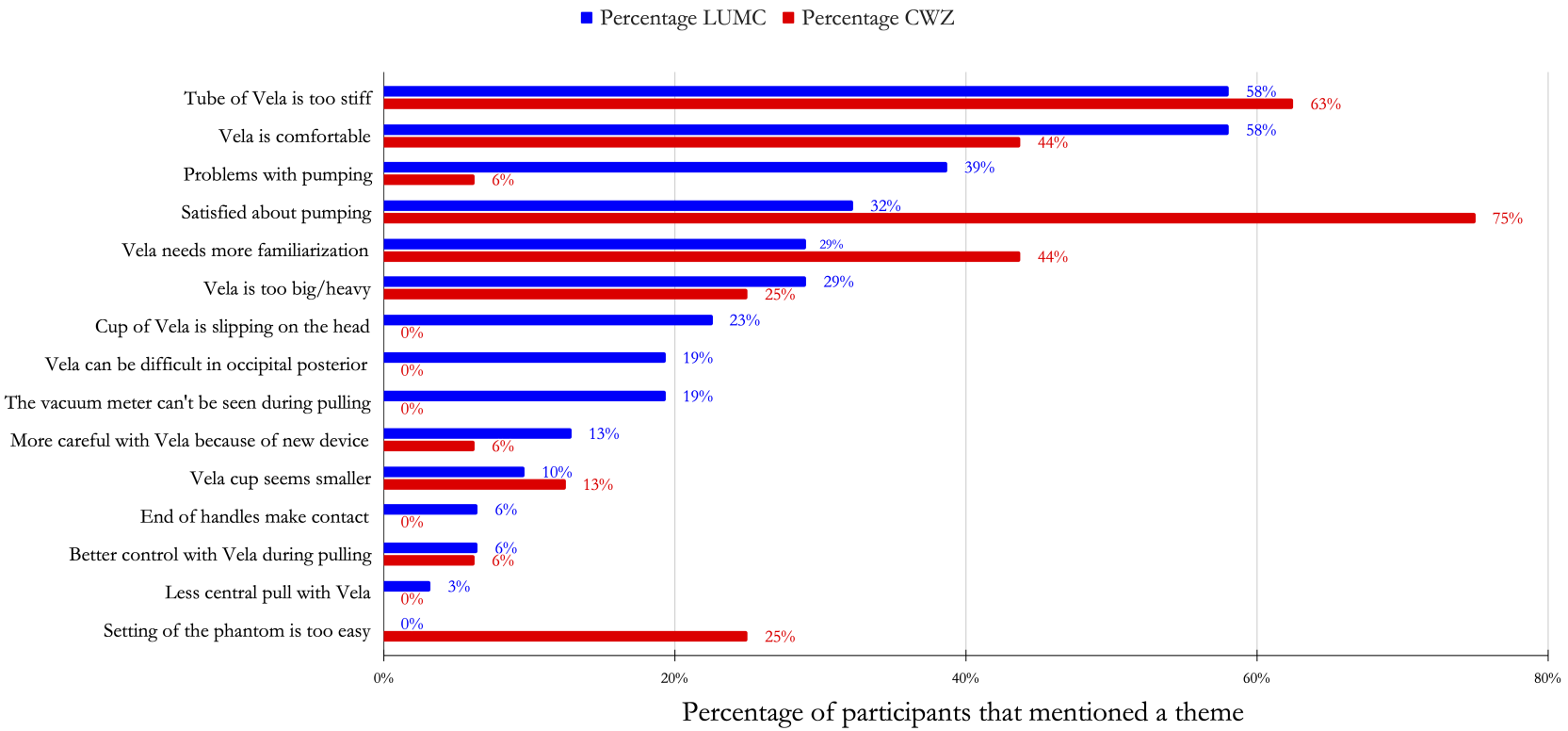


Fig. 9: Responses to the open question *"What is your overall opinion?"* in percentage of all participants that mentioned a theme.

IV. Discussion

This study had the aim of comparing two vacuum extractors, by having experienced obstetricians and residents perform vacuum extractions on a mannequin with both the Vela and the Kiwi Omnicup. The hypothesis was that for the primary endpoint "the number of traction windows needed for successful vacuum extraction", the Vela would be non-inferior to the Kiwi. This hypothesis was substantiated as the Vela was found to be non-inferior for the primary endpoint in both facilities. For all secondary endpoints, no significant differences were found between the Vela and Kiwi, with one exception: in LUMC, the Vela and the Kiwi differed significantly on satisfaction, in favor of Kiwi. For comparison after both vacuum extractions, all averages lie around 2 (Vela and Kiwi are equal). This means that at both LUMC and CWZ, participants found the two devices equal on average for placement, pumping and pulling. Common emergent themes as a response to the open question were the stiffness of the tube, pumping, comfort and familiarization. The positive results regarding the Vela can be explained by the fact that the Vela was appreciated and that the Vela and Kiwi are very similar in terms of placement, pumping and pulling. Additionally, the difference in satisfaction in the LUMC can be explained by the fact that the confidence of the Vela was not yet there, as it was a new device. This was also frequently mentioned by the participants. Furthermore, the satisfaction average for the Vela in LUMC was 2.2, on a scale of 4, where 2 means satisfactory, so the Vela is still close to the satisfaction side, even though participants were significantly more satisfied with the Kiwi.

In the open question analysis, several areas of improvement for the Vela emerged. Many participants mentioned the Vela's stiff tube. Because of the stiff tubing, the Vela can sometimes not be well-placed in difficult foetal positions. Furthermore, participants talked frequently about pumping with the Vela, with varying opinions at CWZ and LUMC, and also within these hospitals. This could be explained by personal preference of pumping method. With the Kiwi, relatively many pumping movements are needed to create the vacuum, compared to the Vela. This is also reflected in the secondary endpoint pumping time. Some participants preferred the fast pumping and others the slow creation of vacuum. In the author's opinion, pumping is a matter of preference and familiarization, as long as a proper vacuum is eventually established. Furthermore, about half of the participants initiated the topic of the positive comfort of the Vela as well as the ergonomics of the device. Many participants commented on the psychology of introducing a new device, stating that familiarization is a factor before complete trust is established. Prior to the vacuum extractions, little instruction was given about the Vela, and participants had only a few minutes to familiarize themselves with the device. In contrast, participants were very familiar and experienced with the Kiwi. Despite the little instruction and practice with the Vela, non-inferiority was still found, which may indicate that the Vela has an intuitive design and is quick to understand.

This study had several strengths and limitations. First, three participants in LUMC were not successful with the Vela, but were successful with the Kiwi. These participants stopped the study on their own initiative after 9, 10 and 12 traction windows with the Vela. Due to this drop out, they were left out of the performance endpoints analysis, therefore the conclusions drawn from this study are only applicable to the sample achieving success with both devices. It is important to realize that these three participants never managed to achieve successful vacuum extraction with the Vela. This may have been due to the fact that there was less confidence with a new device, so these participants may have stopped trying with the Vela sooner, compared to the Kiwi.

Second of all, endpoints were carefully selected through a literature review on relevant endpoints in vacuum extractor validations. However, there were no prior studies comparing vacuum extractors through a mannequin study. The selection of endpoints was therefore a combined process consisting of looking at endpoints used in clinical trials on the one hand, while on the other hand consisting of talking to experts and discussing endpoints for this mannequin study. Ultimately, a substantiated choice of endpoints was made. Both objective performance endpoints and subjective opinion endpoints were measured in this study. These mixed methods enabled the presentation of the Vela as non-inferior to the Kiwi on the one hand, and the collections of clinicians' opinion on the development of the Vela on the other hand. For the statistical analysis, the fact that there were no previous studies made it difficult to choose a non-inferiority limit. Despite these challenges regarding choosing a limit, the choice for the limit of two, was made in extensive consultation with obstetricians. To further substantiate the non-inferiority of the Vela as found in this trial, the standard t-test was executed, which showed that there was no significant difference between the Vela and Kiwi for the primary endpoint.

Furthermore, the mannequin used (Lucy and her Mum) had some limitations for the study. It was challenging to standardize the distribution of the lubricant needed to move Lucy's head through the birth canal. Furthermore, while standardization of positioning Lucy's head in the mannequin was attempted by using tape indications and the same assistant every time, it is difficult to prove that the exact same position was found for each test run. More fundamentally, in CWZ the researchers were confronted with reasons to believe that the same model of the mannequin was in fact differing from the first facility's mannequin, although the model edition was the same. After careful comparison, Lucy's head used to perform the study in CWZ appeared to indent much more. While extensive efforts to standardize across centres were made prior to the study, the findings about the different Lucy's led to the separate analysis of all data. However, since non-inferiority was found in both hospitals, this did not significantly affect the results. Nonetheless, it might have affected the difference between hospitals in terms

of satisfaction, and it might be a reason why in LUMC three participants discontinued the vacuum extraction.

Moreover, the Kiwi's were used multiple times by the participants for financial reasons, despite in real life they are being discarded after one use, because they are not designed to be cleaned. This may have resulted in the Kiwi's not working properly after several uses, even though the Kiwi's were tested in between trials and they did not have to be cleaned.

This was a two-center study, thus the performance and opinions of both hospitals were included. This was especially important for the inclusion of opinions, as protocols or preferences for vacuum extraction may vary per hospital. Additionally, using two centres and therefore two different Lucy's made it possible to perform a difficult and an easy scenario of vacuum extraction, because the head of the mannequin differed in terms of flexibility between hospitals. Therefore, the data of the results are more insightful than when the study was done only in one centre. Moreover, during the opinion survey at both hospitals, data saturation was found, as defined in the article by Guest et al. [17]. This was determined by the fact that in both hospitals, no new information or topics were raised after about twelve participants.

Lastly, for secondary endpoints, data triangulation was used [18]. This was done by considering not only statistical analysis, but also the interpretation and acceptance of confidence intervals from experts at LUMC and CWZ.

To the author's knowledge, this is the first study to validate a vacuum extractor by comparing it to another vacuum extractor in a mannequin study. The importance of validating medical devices is indicated in several prior studies [19] [20]. This study represents one of the first in this particular field of vacuum extractor validations through a mannequin study, and can be taken as an example for mannequin studies. It is also an example of how a well-founded study design can be established despite no previous similar studies.

V. Conclusion

To conclude, the results found suggest that the Vela is non-inferior to the Kiwi when used by experienced obstetricians or residents, since for the primary endpoint non-inferiority was found. Furthermore, no significant differences were found on all secondary endpoints, except satisfaction in LUMC. However, three participants stopped the study with the Vela on their own initiative, making the results applicable only to participants who were able to perform successful vacuum extraction with both the Kiwi and the Vela. The open question showed that there are some recommendations to the Vela, such as a reduction in tube stiffness and more needed familiarization with a new device. Finally, this has been a useful step in proving the efficacy of the Vela and in initiating a follow-up step to further improve the design of the Vela. The next step in the development of the Vela would be a validation in LMIC, as well as research into its usability in terms of cleaning and (dis)assembly.

Acknowledgement

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Research Protocol 3

The following pages show the research protocol submitted to the METC, TU Delft, LUMC and CWZ as part of the ethical approval process.

RESEARCH PROTOCOL

Comparison between the Vela Vacuum Extractor and the Kiwi Omnicup: a randomized mannequin study

Short title	Comparison between the Vela Vacuum Extractor and the Kiwi Omnicup
Version	01
Date	07-10-2022
Coordinating Investigator / Project Leader	Iris Meijer Department of Biomedical Engineering Faculty of Mechanical, Maritime and Materials Engineering (3mE) at the TU Delft
Principal Investigator LUMC	Prof. Thomas van den Akker, MD, PhD Obstetrician, Professor Global Maternal Health Leiden University Medical Center
Principal Investigator CWZ Nijmegen	Dr. Barbara Nolens, MD, PhD Gynaecologist CWZ Nijmegen
Supporting Expert	Dr. Paul Ramler, MD, PhD Resident Doctor Obstetrics & Gynaecology Leiden University Medical Center

SUMMARY

Rationale: In the current era of 'going green', there is an increasing demand for sustainable and affordable medical interventions. Layco Medical Devices has developed a low-cost and reusable vacuum extractor called the Vela (Vacuum Extractor Layco Medical); suitable for both high- and middle- and low-income countries. Before implementation, the Vela vacuum extractor will be compared in a mannequin study with the Kiwi Omnicup, the vacuum extractor currently in use.

Objective: The main objectives of this study are to compare the clinical usability, reliability and effectiveness of the newly designed Vela vacuum extractor with the Kiwi Omnicup.

Study design: This will be a randomized mannequin study in the Leiden University Medical Center and the CWZ Nijmegen hospital in the Netherlands. Participants will perform a vacuum extraction with the Vela and the Kiwi Omnicup and will be randomized according to the device they will use first. The vacuum extraction will be performed on the 'Lucy and her mum' birthing simulator.

Study population: The participants will be obstetricians and residents OB/GYN from the Leiden University Medical Center and CWZ hospital. All participants must be authorized to perform a vacuum extraction with the Kiwi Omnicup in a clinical situation. Since this study is a mannequin study, no labouring women will participate in this study.

Main study parameters/endpoints: Each participant will attempt a vacuum extraction on the "Lucy and her mum" birthing simulator with both the Vela vacuum extractor and the Kiwi Omnicup until successful extraction. During a simulated "traction window" of 25 seconds, the participant is allowed to pull with the vacuum extractor. The primary endpoint is the number of traction windows until the head of Lucy is born. The secondary endpoints are the total number of times the cup of the vacuum extractor detaches during all traction windows, the exact success time of the successful traction window and the pump time in the successful traction window. Subsequently, all participants will be asked to fill in a satisfaction questionnaire.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Participants will perform two vacuum extractions (one with the Vela vacuum extractor and one with the Kiwi Omnicup) and will fill in a questionnaire. This will probably take around half an hour of their time. Participants will not be exposed to any risks.

1. INTRODUCTION AND RATIONALE

A vacuum-assisted birth is a procedure sometimes used to help to deliver the baby when labour is obstructed, prolonged, or during indications of foetal distress. During a vacuum extraction, a cup is placed on top of the head of the baby and firmly attached using negative pressure. During each contraction of the mother, the clinical caregiver pulls the device in order to guide the baby through the birth canal and deliver the baby vaginally.

A vacuum-assisted birth takes places in 7% of all births in the Netherlands[1]. In 2001, Aldo Vacca, an obstetrician from Australia, introduced the Kiwi Omnicup[2]; a small handheld plastic vacuum extractor that since its introduction is widely used in high-income countries[3].

However, the Kiwi Omnicup is not reusable and too expensive to be implemented in low- and middle-income countries. There are some reusable vacuum extractors, but these devices are not easy to use and high in price. In both high- and low- and middle-income countries, there is a need for a reusable and affordable vacuum extractor with regard to sustainability as well as to lower the neonatal morbidity and mortality in low- and middle-income countries.[4,5]

Therefore, Layco Medical Devices started working on a new vacuum extractor that is reusable and will be low in price. This vacuum extractor device is called the Vela (Vacuum Extractor Layco Medical). Because of its reusable design, the costs of each vacuum-assisted birth are estimated to be lower compared to the Kiwi Omnicup. Layco Medical Devices strives for the Vela vacuum extractor that is as good as the Kiwi Omnicup. For this reason, we designed a randomized mannequin study to compare the Vela vacuum extractor with the Kiwi Omnicup.

[1] *Perined*. (n.d.). Kerncijfers Nederlandse Geboortezorg 2020. Retrieved July 21, 2022, from https://www.perined.nl/onderwerpen/publicaties-perined/kerncijfers-2020

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2. OBJECTIVES

The objective of this study is to compare the Vela vacuum extractor with the Kiwi Omnicup in order to answer the following research question: is the Vela vacuum extractor not worse (non-inferior) to the Kiwi Omnicup?

3. STUDY DESIGN

This is a randomized mannequin study in the Leiden University Medical Center and the CWZ Nijmegen hospital. The participants will be obstetricians and residents authorized to perform a vacuum-assisted birth with the Kiwi Omnicup. The vacuum-assisted births in this mannequin study will be performed on the "Lucy and her mum" mannequin (Model Med). Each participant will perform a vacuum extraction with the Vela vacuum extractor and the Kiwi Omnicup. Participants will be randomized according to the vacuum extractor they will use first. Additionally, the opinion of the participant will be asked.

4. STUDY POPULATION

No patients will participate in this study as this is a mannequin study. Only obstetricians and residents will participate in the vacuum extractions.

Population (base)

The participants will be obstetricians and residents from the Leiden University Medical Center and the CWZ Nijmegen hospital that are authorized to perform vacuum-assisted births. All obstetricians and residents from these hospitals will be asked to participate in this study by the principal investigators and will receive an information sheet that explains the study and will sign an informed consent.
No labouring women will participate in this study.

Inclusion criteria

Participants must meet the following criteria:

- The participant is an obstetrician or resident working in the Leiden University Medical Center or the CWZ Nijmegen hospital.
- All participants must be authorized to perform a vacuum-assisted birth with the Kiwi Omnicup.

Sample size calculation

The sample size is calculated using a sample size calculation for continuous outcomes in non-inferiority trials. The sample size is calculated based on the primary endpoint, number of traction windows until successful delivery. The null hypothesis (H_0) is defined as: the Vela is inferior to the Kiwi Omnicup, with a non-inferiority limit (d). The alternative hypothesis (H_a) is defined as: the Vela is non-inferior to the Kiwi. Together with an obstetrician and a resident, a non-inferiority limit of $d = 2$ was chosen. This means that it is still clinically acceptable that the Vela performs a successful vacuum extraction in 2 traction windows more than the Kiwi. This limit was chosen because during an actual vacuum extraction, the obstetrician usually pulls during 3 contractions, before he/she moves to a caesarean section. So a maximum of 2 contractions/traction windows difference can still mean a successful overall vacuum extraction.
Because there are no prior studies comparing two vacuum extractors in a mannequin study, the standard deviation had to be estimated. In order to do this, a test-run was held inside the LUMC, by performing five vacuum extractions on the Lucy mannequin. From this experiment, a standard deviation (σ) of 1.81 traction windows was found for the difference between Vela and Kiwi.
With a significance level (α) of 0.05, a power ($1-\beta$) of 0.9, a non-inferiority limit (d) of 2 and a standard deviation (σ) of 1.81, the sample size calculation was performed.
With the power size calculator of the Minitab® Statistical Software, it was calculated that a minimum of 9 participants were needed to be 90% sure that the upper limit of a one-sided 95% confidence interval will be below the non-inferiority limit of 2.

5. INVESTIGATIONAL AND COMPARATOR PRODUCT

The investigational product is the Vela Vacuum Extractor (2022) developed by Layco Medical Devices. This is a newly designed low-cost reusable vacuum extractor. The main new feature is the reusable nature of the device, because the device is easily disassembled, which ensures that the various components are easy to clean and reassembled again. Therefore, the various components can also undergo different cleaning techniques.

The comparator product is the Kiwi Omnicup[6] (2000) designed by Aldo Vacca. This device is a single-use disposable vacuum extractor. This vacuum extractor was chosen as a comparator product, because it is a widely used device used during vacuum-assisted births. The Kiwi Omnicup is the standard device during vacuum-assisted births in the Leiden University Medical Center and the CWZ Nijmegen hospital.

[6] Vacca, A. (2000). Clinical evaluation of a new obstetric vacuum extraction device. Obstetrics & Gynaecology, 95(4), S43.

6. METHODS

Study parameters/endpoints*

*These parameters were partially established by executing a literature review: *'An Insight into Relevant Endpoints in Vacuum Extractor Validation Studies'.*

- **Main study parameter/endpoint**

The primary endpoint is the number of traction windows until successful vacuum extraction. A successful vacuum-assisted birth means that the head of the mannequin baby has been exerted with the guidance of either the Vela vacuum extractor or the Kiwi Omnicup within the traction window.

- **Secondary study parameters/endpoints**

The secondary endpoints are:

- Number of pop-offs of the cup: number of times the cup is fully detached from the head of Lucy during all traction windows.
- Duration (measured in seconds) of successful traction window: the number of seconds until success in the successful traction window. This "success time" is measured from the beginning of the traction window until Lucy's head is exerted.
- Duration of pumping time in successful traction window: the time of pumping until the correct negative pressure is reached on the head of Lucy before the successful traction window.
- Satisfaction after each successful vacuum extraction, on a scale of 1-4 (extremely satisfactory - extremely unsatisfactory), assessed through a questionnaire.
- Opinion after both vacuum extractions, on a scale of 1-3 (Vela is better-equal-worse than Kiwi), for every category:
  - Placement
  - Pumping
  - Pulling
- Open question: "What is your overall opinion on the Vela and differences compared with the Kiwi?"

Randomization, blinding and treatment allocation

All participants will perform a vacuum extraction on the 'Lucy and her mum' mannequin with the Vela vacuum extractor and the Kiwi Omnicup until a successful vacuum-assisted birth is completed. The order in which the participants will perform the vacuum extraction with the Vela vacuum extractor or the Kiwi Omnicup will be determined by a computer-generated list randomizer. Two scenarios will be inserted in the list randomizer for each participant separately:

- Vela first
- Kiwi first

As a result, the randomizer assigns the participants to a vacuum extraction order at random.

Study procedures

This study will take place in both the Leiden University Medical Center and the CWZ Nijmegen. The procedure will be the same for both hospitals.

- **Start of the experiment**

The participants will be assembled in a room and the coordinating investigator will provide essential information about the study. All participants will read and sign the informed consent. Hereafter, the participants will one-by-one go to the experiment room. There will be time to get familiarized with the Lucy mannequin, Vela and Kiwi.

- **A vacuum extraction**

The procedure will be the same for both the vacuum extraction with the Vela and with the Kiwi.
There can be two options of order*:

1. First vacuum extractor is Vela
2. First vacuum extractor is Kiwi

*the order will be determined by randomization

The participant will be handed the vacuum extractor (Vela or Kiwi). Then, the participant is asked to perform a vacuum extraction on the 'Lucy and her mum' mannequin with the given vacuum extractor device.

Figure 1: Lucy and her mum birthing simulator[7]

The Lucy mannequin will be lubricated with water-based lubricant before every vacuum extraction. A researcher will position the head of Lucy inside the mannequin in occiput anterior position. The participant will put the cup of the given vacuum extractor inside the mannequin and attach it to the head of the baby by creating negative pressure with the hand-pump. If the vacuum extractor cup is correctly placed, the simulated traction window will start. This is simulated as a timeslot of 25 seconds in which the participant is able to pull the head out of the mannequin. After this window, a pause of 10 seconds will take place. Then, a new traction window of 25 seconds will start. When a pop-off occurs, that traction window has failed and the new traction window will start. During the traction, the

[7] Lucy Instrumental Birth Simulator. (n.d.). Paradigm Medical. Retrieved July 13, 2022, from https://www.paradigmmedicalsystems.com/lucy-1

eventual birth will be facilitated solely by the force of the participant: thus, a researcher will **not** push along at the back of the mannequin. When the head is exerted, the traction window is successful and completed. In the flowchart on the next page, the procedure can be seen.

After each vacuum extraction, a rating question will be asked on the overall opinion of that particular device: "On a scale of 1-4, how satisfactory did the device perform?".

Several things can happen during a vacuum extraction.

- When 25 traction windows have occurred, the vacuum extraction with that device has failed and a maximum of 25 windows will be noted.
- When the Vela or Kiwi breaks during a traction window, a spare device will be handed to the participant and the traction window may be re-done.

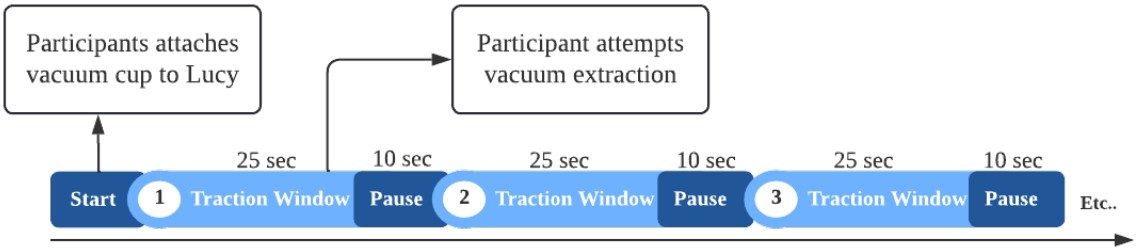

Figure 2: Flowchart of a vacuum extraction with one device

- **After both vacuum extractions**

After both vacuum extractions with the Vela vacuum extractor and the Kiwi Omnicup, the participant's overall opinion is asked about both devices. These answers will be audio-recorded and transcribed after the experiment. Lastly, 3 additional rating questions will be asked and one open-ended question will be asked.

After both vacuum extractions:

- What is your overall opinion of the Vela and the difference compared to the Kiwi?

After both vacuum extractions:

- On a scale of 1-3 (better/equal/worse), how was the **placement** of the Vela in comparison with the Kiwi?
- On a scale of 1-3 (better/equal/worse), how was the **pumping** of the Vela in comparison with the Kiwi?
- On a scale of 1-3 (better/equal/worse), how was the **pulling** with the Vela in comparison with the Kiwi?

Withdrawal of individual subjects

Participants can leave the study at any time for any reason if they wish to do so without any consequences.

7. SAFETY REPORTING

No labouring women will participate in this study. The participating obstetricians and residents will not be exposed to any risks and therefore adverse events are not applicable for this study.

8. STATISTICAL ANALYSIS

Primary study endpoint

- Number of traction windows until successful vacuum extraction (#)

This parameter is a continuous variable. The data will be presented with means and standard deviations. This parameter will be analysed using a one-sided paired samples t-test with a non-inferiority limit of 2 traction windows.

Secondary study parameter(s)

- Number of pop-offs of cup (#)
- Time of successful traction window (seconds)
- Time of pumping in successful traction window (seconds)

These are all continuous variables. Means and standard deviations shall be reported. They will be analysed using a two-sided paired samples t-test. Data will be analysed for significant difference between Vela and Kiwi.

- Satisfaction question

This is an ordinal variable. Means and standard deviations shall be reported. The 4-point Likert scale question will be analysed using a two-sided paired samples t-test. Data will be analysed for significant difference between Vela and Kiwi.

- Comparison question

The comparison question (1-3) will be presented with means of placement, pumping and pulling. Means of the three categories will be presented.

- Open question

Qualitative input generated by the transcription of the open question shall be analysed by identifying overarching themes and counting their occurrence. Recurring themes will be presented, together with their occurrence on how many % of the participants initiated this theme.

9. ETHICAL CONSIDERATIONS

Recruitment and consent

The recruitment will be done by both principal investigators at the LUMC and the CWZ Nijmegen hospital. In the gynaecology department, obstetricians will be invited to join this study. Potential participants will have a week to consider their participation.

Participants are protected from involuntary actions by signing the informed consent form and being able to leave the study at any time. The anonymity of the data will make sure the participant feels protected and experiences no pressure.

Written consent to participate in the study will be obtained from all participants prior to the start of the study by the investigator through an informed consent form. This form will provide information about the study, including an opening statement, which will outline the purpose of the research and what participants will do. Each form will be signed by the investigator and the participant prior to the experiment.

10. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

Handling and storage of data and documents

All anonymized data will be preserved for 10 years and only the coordinating investigator and principal investigators will have access to the source data. The anonymized data will also be collected in the TU Delft OneDrive. There will be direct entry for all primary and secondary measurement points.

Temporary halt and (prematurely) end of study report

The project leader does not see any potential circumstances for ending the study (prematurely). The participants are free to leave the study any time. They will be excluded from the results.

11. REFERENCES

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Study Design Rationale | 4

This is an additional chapter to substantiate this thesis. In this chapter, a rationale is given for the main choices of this study. These choices concern the study protocol and design of the study.

4.1 Study Design

This study was set up as a non-inferiority study. This was done for a couple of substantial reasons. The Vela was initially designed for LMIC. The reason for developing the Vela was not to be superior to the Kiwi in aspects such as performance, but to provide LMIC with a proper alternative that fits into the local context and is cost-effective. Because the Vela is simple and reusable, it can be seen as superior to the Kiwi in LMIC. More so, it can even be seen as superior in high-income countries in terms of sustainability reasons. However, an important aspect is that the performance quality of the Vela should not detract from today's gold standard: the Kiwi Omnicup. Hence, the aim of this study was to validate whether the Vela is non-inferior to the Kiwi. That means that the Vela is at least no worse than the Kiwi, i.e. equal or better.

Furthermore, this study was conducted on a mannequin. The decision to not yet conduct a proper clinical study, i.e. not to conduct the study on patients, was a deliberate one. Firstly, because the current state of the Vela is still a prototype. This study is the first real study to investigate the efficacy of the Vela and the safest way to do this is on a mannequin. A first clinical study would be appropriate at a later stage of the Vela, when several tests have been done that give assurance that the device is sufficient for a real delivery. Moreover, a mannequin study is an easier, cheaper and faster type of study than a patient study. The aim of this study was to investigate the efficacy of the Vela, but also to gather participants' opinions. The latter was easy to do during a mannequin study, because the participant could already give their opinion while performing the vacuum extraction. In a patient study, the procedure revolves more around the patient, who is in labour, than around the device. Furthermore, in a shorter time, more participants could have a turn compared to a clinical trial, during which you would have to wait until a vacuum extractor is needed for a delivery. Also, in a mannequin study, one participant can perform a vacuum extraction with both devices, making it easier to compare results.

4.2 Endpoints

Since there are no previously published studies validating the two vacuum extractors in a mannequin study, a different way of establishing endpoints than looking at prior studies had to be determined. As a

solution, an insight was created into clinical studies validating one or more vacuum extractors. A systematic review was conducted in which endpoints were established, and extent of relevance was determined. This literature review can be found in Appendix A [1]. The translation from clinical studies to mannequin studies was then performed, done by looking at the relevant endpoints found in the literature and then determining whether these endpoints could be measured on a mannequin that simulated birth. This yielded the following endpoints:

1: See the literature review: An Insight into the Relevance of Endpoints in Vacuum Extractor Validation Studies: A Systematic Review.

- Number of traction windows/contractions
- Number of pop-offs
- Vacuum extraction time

Additionally, there was also extensive consultation with clinical experts at LUMC, working in the field of vacuum extraction, during the design of the study. Together with them, a number of additional endpoints were added to the parameters. These were the following endpoints:

- Pumping duration
- Satisfaction after vacuum extractions
- Comparison between devices after vacuum extractions

Adding the opinion questions provided a good trade-off between device performance and participant opinion. Both topics were perceived as equally important by the clinical experts. Especially in this stage of the development of the Vela, wherein the Vela is still a working prototype, it is important to include the opinion of the obstetricians and residents into the design.
Ultimately, consultation with the clinical experts resulted in the following primary endpoint: the number of traction windows/contractions until successful vacuum extraction. This is because, this endpoint indicates the most clinical relevance for the comparison between the Vela and the Kiwi. Also, this endpoint tests well for non-inferiority between devices.

4.3 Participant Group

The participants in this study had to meet a number of requirements. First of all, they had to be obstetricians or residents and secondly, they had to have authorisation to carry out a vacuum extraction. This group of participants was deliberately chosen so as to include people with experience in vacuum extraction. As the development phase of the Vela is currently in progress, i.e. a working prototype, it was deliberately decided to include experienced participants, because their opinions could provide interesting points of view.
If less experienced participants had taken part, there might have been a risk that the emphasis would have been on the learning curve of the participants rather than the efficacy of the devices. This could have led to a big difference depending on which device the participant started with. Which could have been rectified by randomization, but it was decided to avoid this problem in advance by solely choosing experienced participants.

4.4 Materials

4.4.1 Lucy and Lucy's Mum

Because no mannequin studies validating a vacuum extractor had been published prior to this study, no example could be taken from previous research for choosing an appropriate birth simulator. In this section, the choice of birth simulator is substantiated.

This mannequin study used the Lucy and her Mum Instrumental Delivery Trainer (Model Med, Victoria, Australia). This mannequin consists of a doll of a baby head (Lucy) and a doll of the lower body of a mother (Lucy's Mum). This simulator is used at LUMC and CWZ Nijmegen to train obstetricians and resident doctors with vacuum extractions. It is a simple mannequin, where the emphasis during training lays on correct placement of the vacuum extractor, creation of the correct negative pressure and proper delivery of Lucy's head. In consultation with the principal investigator of the study from LUMC and the supporting investigator, it was determined that this simulator is a sufficient mannequin to test the main objective of this study. The main objective of this study was to compare the effectiveness of the Vela to the Kiwi Omnicup on the one hand, and on the other hand to collect the opinions of obstetricians and residents on the comparison between the Vela and the Kiwi. The first part of the objective is measurable through most endpoints. It was determined beforehand through a test-run that all these endpoints could be measured well during a vacuum extraction on the Lucy mannequin. The second part of the objective, the opinion of the participants, could also be captured well by using the Lucy. All necessary actions on which questions would be asked take place during a vacuum extraction on the Lucy.
Additionally, during the choice of mannequin, there were also discussions about choosing for a more advanced mannequin in which contractions are simulated. This more advanced simulator could only be found in a training center. No experienced obstetricians or residents would be present in this training center, meaning the study would be conducted using less experienced participants. Partly because of this, it was ultimately decided to conduct this study with the simpler mannequin (Lucy and her mum) and include more experienced participants, rather than an advanced mannequin but less experienced end-users. This was also decided because the opinion of the participants is an essential aspect in this study.

Figure 4.1: The Lucy and her Mum Instrumental Delivery Trainer [8].

4.4.2 Vela^{TM}

In the study, the main objective is to investigate whether the functioning of the Vela is non-inferior to the Kiwi Omnicup. In this sense, the main device under investigation is the Vela, a novel type of vacuum extractor developed by Layco Medical Devices. Due to patent-sensitive reasons, the specifications of the Vela cannot be explained further than is done in the paper.
But in the run-up to and preparation for this study, I also helped to make some modifications to the Vela. Namely, I set up a test day of the

Figure 4.2: A picture of the **old prototype** of the Vela [9].

study design and a feedback day on the device design at LUMC. From this feedback we gathered during these days, the design of the Vela was adapted several times to satisfy obstetricians' needs. For example, the handle size of the Vela was reduced during this feedback session, a pressure gauge was added, a spring was incorporated, improving pumping, and we were alerted to unevenness in the design. After the test day of the study protocol, we changed the handle material from UV curable Resin to PETG after the handle broke during testing. From this, we concluded that the material needed to be stronger. We also changed the design of the cup, ensuring the cup would remain on the tube during load. Moreover, these points of feedback on the design did not come up again during the real study, indicating this feedback was handled correctly.

4.4.3 Kiwi Omnicup

This study validates the Vela prototype by doing a non-inferiority comparison with the Kiwi Omnicup. Of course, there are many different vacuum extractors used in practice. Nevertheless, the Kiwi Omnicup was chosen for a number of reasons. First, the Kiwi is the standard method for vacuum extractions in the hospitals where this study was conducted. If the Vela were to come out of the test as non-inferior in this study, this would allow the statement to be made that the Vela is non-inferior to the gold standard of these hospitals, substantiating the efficacy of this Vela prototype.
Second, in terms of features, the Kiwi is very similar to the Vela. For instance, they are both hand-held and hand-pump devices. Also, they both have a rigid cup, a pressure gauge and are close in size. For comparing the Vela, this similarity between the Kiwi is relevant because it allows for comparison on more substantive details, rather than differences in functionality of the devices.
Finally, the efficacy of the Kiwi has already been demonstrated in many clinical trials in the literature [4, 11–15]. Comparing the Vela to such a well-proven device would strengthen the claim about the Vela's efficacy.

Figure 4.3: The Kiwi Omnicup, developed by Clinical Innovations [10].

4.5 Statistics

4.5.1 Sample Size

For the sample size, an extra rationale is presented here. In the research protocol, the following calculation of the sample size is provided:

"The sample size is calculated using a sample size calculation for continuous outcomes in non-inferiority trials. The sample size is calculated based on the primary endpoint; number of traction windows until successful delivery. The null hypothesis (H_0) is that the Vela is inferior to the Kiwi Omnicup, with a non-inferiority limit (d). The alternative hypothesis (H_a) is defined as: the Vela is non-inferior to the Kiwi. Together with an obstetrician and a resident, a non-inferiority limit (d) of $d = 2$ was chosen. This means that it is still clinically acceptable that the Vela performs a successful vacuum extraction in 2 traction

windows more than the Kiwi. This limit was chosen because during an actual vacuum extraction, the obstetrician usually pulls during 3 contractions, before he/she moves to a caesarean section. So a maximum of 2 contractions/traction windows difference can still mean a successful overall vacuum extraction.
Because there are no prior studies comparing two vacuum extractors in a mannequin study, the standard deviation had to be estimated. In order to do this, a test-run was held inside the LUMC, by performing a couple of vacuum extractions on the Lucy mannequin. From this experiment, a standard deviation (σ) of 1.81 traction window was found for the difference between Vela and Kiwi. With a significance level (α) of 0.05, a power (1-β) of 0.9, a non-inferiority limit (d) of 2 and a standard deviation (σ) of 1.81, the sample size calculation was performed. With the power size calculator of the Minitab® Statistical Software, it was calculated that a minimum of 9 participants were needed to be 90% sure that the upper limit of a one-sided 95% confidence interval is be below the non-inferiority limit of 2."

In this subsection, a rationale is given for the estimation of the standard deviation of this sample size calculation. Because there are no prior studies comparing two vacuum extractors in a mannequin study, the standard deviation had to be estimated in order to calculate the sample size. This was done by conducting a pilot study during a consultation we had in the LUMC with obstetricians. In this pilot study, the obstetricians attempted five vacuum extractions both with the Vela and the Kiwi. From this data, an estimate could be made about the amount of traction windows it would take to have a successful delivery with both devices. From this data, the standard deviation of the difference between the Vela and Kiwi could be made. The pilot resulted in the following data:

Trial	Traction Windows with Vela	Traction Windows with Kiwi
1	6	3
2	2	2
3	2	3
4	4	5
5	3	1

From this data, the standard deviation was calculated by deducting the amount of traction windows of Vela minus Kiwi, and then calculating the standard deviation of these five values using Excel. This resulted in a standard deviation of the difference between the two devices of 1.81.

4.5.2 Analysis in R

For the statistical analysis, the R software (version R 4.2.2) was used for performing the statistical tests for the primary and secondary endpoints. This programming language was used because the statistical tests can be written by the users themselves. This was preferred over SPSS or Excel, in which only a standard number of tests could be chosen from. For the non-inferiority design of this study, it was necessary to write the specific statistical test code.

Primary Endpoint

In the figure below, the R script can be seen for the analysis of the primary endpoint in the LUMC.

```
data = read.csv(file = "Downloads/R/Contr LUMC/data_Endpoint_1.csv", sep = ";")

t.test(x = data$Vela.contr.LUMC,
       y = data$Kiwi.contr.LUMC,
       paired = TRUE,
       mu = 2,
       alternative = "less")

```

Figure 4.4: R script for statistical analysis of primary endpoint in LUMC.

In this script, a one sided paired samples t-test was conducted. Meaning that for one tail, the data was analyzed to check if the difference between the Vela and the Kiwi lies within the non-inferiority limit of 2 traction windows. The test was a paired samples t-test, meaning that for every participant, the data was coupled. So first, the difference between the Vela and the Kiwi was determined per participant and this data was then analyzed. For the difference, the following calculation was used:

Difference = Vela - Kiwi

For the t-test, the following null hypothesis and alternative hypothesis were defined:

H_0 : *Difference (Vela - Kiwi) is above the non-inferiority limit of 2*
H_a : *Difference (Vela - Kiwi) is below the non-inferiority limit of 2*

In other words, these hypotheses can be stated as:

H_0 : *Vela in inferior to the Kiwi Omnicup*
H_a : *Vela is non-inferior to the Kiwi Omnicup*

The hypotheses are reversed compared to a standard t-test, because this study aimed to analyse non-inferiority, rather than superiority.

This R-script was used to compute a p-value for the primary endpoint, in both CWZ Nijmegen and LUMC. If the p-value was below or equal to the significance level (α) of .05, the null hypothesis must be rejected and the alternative hypothesis may be accepted, concluding that the non-inferiority is proven for the primary endpoint of this study.

Secondary Endpoints

For the secondary endpoints, no non-inferiority limits were established beforehand. It was decided to analyse the secondary endpoints without non-inferiority limits and thus with a standard two sided paired samples t-test. Using this test, insights can be created in terms of significant difference between the two devices. The difference was calculated in the same manner as for the primary endpoint (Vela - Kiwi). For this standard t-test, the hypotheses are defined as follows:

H_0 : *There is no significant difference between Vela and Kiwi*
H_a : *There is a significant difference between Vela and Kiwi*

```r
data = read.csv(file = "Downloads/R/Popoff LUMC/R programming - Pop off LUMC.csv", sep = ";")

t.test(x = data$Pop.off.Vela,
       y = data$Pop.off.Kiwi,
       paired = TRUE,
       mu = 0,
       alternative = "two.sided")

```

Figure 4.5: R script for statistical analysis of a secondary endpoint in LUMC.

When a p-value lower or equal than the significance level was found ($p \leq .05$), the null hypothesis is rejected and the alternative hypothesis is accepted. When the p-value is higher than the significance level, the null hypothesis may not be rejected, and there can be concluded that there is no significant difference between the Vela and the Kiwi.

4.6 Learning Curve

In order to examine the learning curve of both devices, there was an extra section of the study in the CWZ Nijmegen. This section took place after the regular study procedure, in a way that it had no effect on the main research. In the extra section, participants were asked to look for successful vacuum extraction two extra times with the last device that was allocated to them in the randomization. If the last device was the Vela, the participant was asked to perform two extra successful vacuum extractions with the Vela and the performance endpoints were measured during these extra vacuum extractions. From this, a potential learning curve could be analysed, by comparing the results of the endpoints between the first and the second vacuum extraction and the second and the third vacuum extraction. This allowed observing learning effects if participants practised vacuum extraction more often.
However, a limitation for observing the learning curve occurred. In the CWZ Nijmegen, the “easy" scenario of the study took place, because of the different head of Lucy used. This resulted in the participants finding success quickly the first time and thus little learning curve could be present in the second and third attempts, as the first time was already successful. This was the case for both the primary endpoint and the performance secondary endpoints (success time and pumping time). It was therefore chosen to leave the learning curve part out of the scientific article. Below, the results are presented for the learning curve analysis. Moreover, non-significant differences were found in the statistical analysis for all measured endpoints between first and second and second and third time success with the Vela. This statistical analysis was done with a standard t-test.

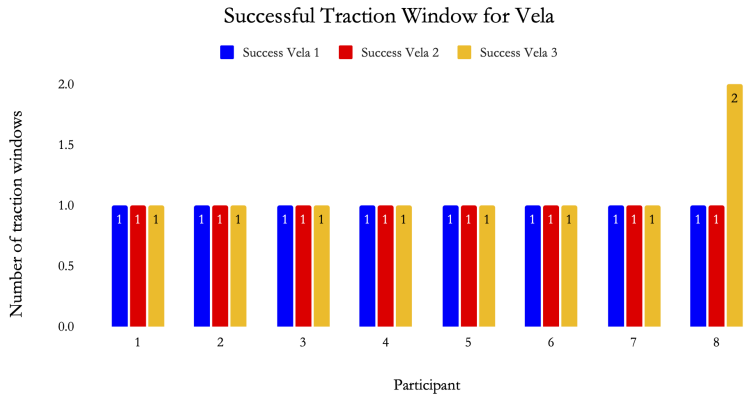

Figure 4.6: The successful traction window per participant for the first, second and third attempt for success with Vela.

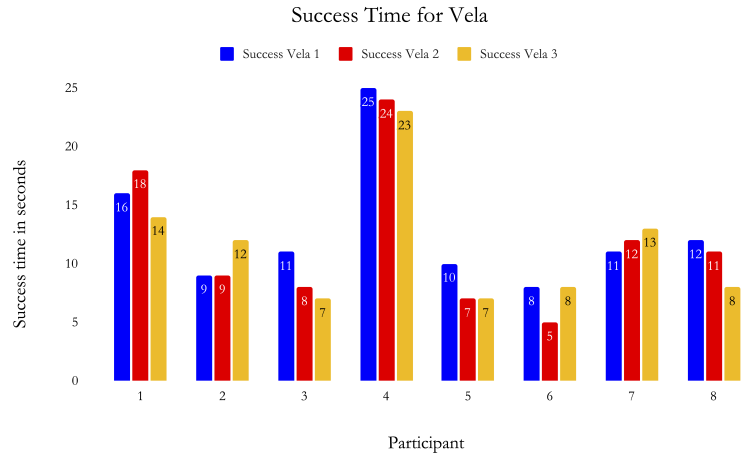

Figure 4.7: The success time per participant for the first, second and third attempt for success with Vela.

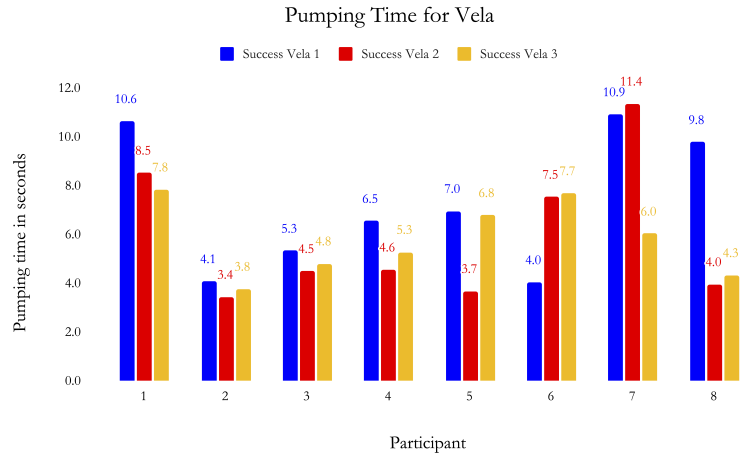

Figure 4.8: The success time per participant for the first, second and third attempt for success with Vela.

Reflection 5

In this chapter, a reflection is given regarding the study choices and outcomes. Topics are debated on whether a better choice could have been made that would have taken this study to a more significant level.

5.1 Location of Study

The Vela was developed out of a primary drive to make medical equipment available and accessible in low- and middle-income countries. When the Vela is introduced on the market, it is important that the device is in any case applicable for LMIC. However, this study took place in the Netherlands; a high-income country. Although, the Vela also offers a promising prospect for high-income countries because of sustainability reasons, in hindsight it can be discussed whether the first mannequin study should have taken place in LMIC. In retrospect, a mannequin study of the Vela in a LMIC would have offered much value. However, the choice to perform this mannequin study in two hospitals in a HIC was made for a number of reasons.
Foremost, the developer of the Vela is a Dutch company, Layco Medical Devices. Layco's network is therefore Dutch and an initial study design in the Netherlands was a logical choice. Furthermore, these two hospitals were close to the development site of the Vela, which allowed for quick anticipation, should the study or device fail. In addition, financially research in the Netherlands was the only viable option.
Moreover, the study setting in the hospitals in the Netherlands could be inspected in advance, providing for a test-run and an examination of the materials used. Allowing for quality control regarding setting and insight into willingness to participate.

Figure 5.1: Image of the test-run in the LUMC, wherein obstetrician Prof. Dr. van den Akker attempts a vacuum extraction with the Vela™.
Note that the head is not being pushed along at the back of the mannequin during a contraction. The researcher merely makes sure the head of Lucy does not fall out from the other side.

Also, the two hospitals in the Netherlands were suitable for comparing the Vela to the Kiwi Omnicup. As the Kiwi is the method of choice in both hospitals, a non-inferiority study might show that the Vela could become an accepted method of vacuum extraction. Allowing for a well-supported conclusion on the effectiveness of the Vela.
As a follow-up study, a validation mannequin study in an LMIC would be the logical next step. One recommendation would be to place more emphasis on user opinion and device usability.

5.2 Choice of Mannequin

This mannequin study was performed on the Lucy and her Mum Instrumental Delivery Trainer [1]. This simulator is used to practice vacuum extractions and was chosen for this study partly for this reason, see Section 4.4. In reflection, it can be debated whether this mannequin was the most suitable for this validation study. In this study, the focus of the endpoints was on the effectiveness of the Vela, but also on the opinion of

1: See figure 4.1.

the end users. For the opinion of the end users, the Lucy mannequin was a suitable simulator. Birth was simulated realistically enough to form an opinion about the devices in terms of placement, pumping and pulling.

However, for the endpoints related to device performance, the mannequin fell short in some aspects. Firstly, Lucy's head could not be placed in the mannequin in exactly the same position every time. The head was placed in the same position each time by same the researcher and this position was approved by a clinician. However, due to human error, the position may have been slightly different, which could have caused differences in the results. In hindsight, a mannequin where the head is placed in the exact same position each time would have been a more suitable option.
Another aspect of the Lucy mannequin is that quite a lot of gel is needed to enable vacuum extraction. This is stated in the doll's instructions for use. As the exact influence of the gel is not clear, it is difficult to make a statement to what extent the gel affected the results. But the fact the gel was needed and the amount could not be standardized was a definite limitation.
Furthermore, no contractions could be simulated with this doll. Usually during training vacuum extractions with this mannequin, someone always pushes along at the back of the mannequin to simulate a contraction. In this study, we chose against this as it would affect the results too much. Resulting in a participant solely having to get Lucy's head out of the mannequin on his/her own. By not simulating contraction force from within, the study setting is less realistic compared reality, this could have affected all efficacy endpoints.

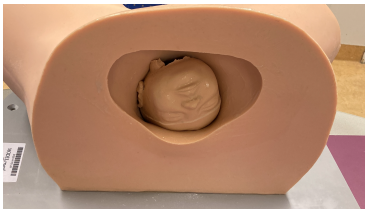

Figure 5.2: Head of Lucy in LUMC.

Figure 5.3: Head of Lucy in CWZ.

Lastly, the head of Lucy differed greatly in the LUMC and the CWZ. The heads should have been the same, because they came from the same manufacturer of the Lucy mannequin (Model Med), however they differed in terms of impressionability. The head from Lucy that was used in the CWZ was more indented and more flexible compared to the one in LUMC. This caused vacuum extractions at the CWZ to be much easier affecting the primary endpoint; pop offs and time required for vacuum extraction. This left room for influence on the participants opinion. Therefore, the decision was made to analyse the data from LUMC and CWZ separately. In the end, one can say that an easy scenario played out in the CWZ and a difficult one in the LUMC. Reflecting, an addition could have been to have the participants also perform the easy scenario in LUMC and the difficult scenario in CWZ. This format of a cross-over study would have been even more insightful.

5.3 Future Recommendations

After this research, the first prototype of the Vela was validated in a mannequin study and the results suggest that the Vela is non-inferior to the Kiwi. Before the Vela is introduced in market, further research and development is needed. The initial purpose for the Vela is to enter the market of low- and middle-income countries and for this a study in LMIC is an important and insightful goal. Here I would suggest performing a study similar to this mannequin study, with the goal of collecting performance and opinions in LMIC, to improve the design of the Vela.

It is also insightful to identify any differences in technique of clinicians and equipment between an HIC (The Netherlands, where this study was conducted) and an LMIC.
In the mannequin study, I mainly looked at the difference between the Vela and the Kiwi in terms of performance and the opinion of the end users. An important part of the Vela is its re-usability and assembly . The idea is that the Vela should be easy to clean, enabling reuse. For this, I recommend conducting a research focusing on the cleaning opportunities and the assembly and disassembly of the Vela.
Furthermore, proper handling of the Vela is also essential. For this, it is important to create clear instructions for use, such as a video or user manual. This builds more familiarization among end users and can be important in successfully performing vacuum extractions.
Once the Vela has a well-validated prototype and it is injection moulded, clinical trials can be carried out. This is an important step in obtaining clinical feedback and validate that the Vela's performance in real life is also optimal, as these results are more reliable than a mannequin study.

Appendix

Literature Review A

This literature review has already been graded by the supervisors.

The following pages contain the literature review 'An Insight into Relevant Endpoints in Vacuum Extractor Validation Studies'.

An Insight into Relevant Endpoints in Vacuum Extractor Validation Studies

A Systematic Review

Iris Meijer (4595424)
Biomedical Engineering – Technical University of Delft
Layco Medical Devices
Supervisors: Prof. dr. J. Dankelman & D. Drexhage
June 8, 2022

Abstract*—*Introduction: **In case of prolonged or obstructed labour, vacuum assisted delivery is a technique that may help facilitate vaginal birth. Vacuum extraction involves guiding the fetus out of the birth canal using a vacuum extractor (VE). In order for this procedure to go as smoothly as possible, the used VE needs to perform optimal. To ensure optimal performance, VEs can be validated. This is frequently done by means of clinical validation studies, in which end-points are measured. The aim of this systematic review was to create an insight into these end-points. Furthermore, a recommendation was made on the most important primary end-points on the basis of incidence and harmfulness.**
Methods: **Two search methods were used for this review. First, scientific articles validating VEs were searched, and second, reported incidents with a VE from the FDA database were searched. Various end-points were gathered, which were sorted according to their incidence and harmfulness. Finally, based on these aspects, an advice was given on which end-points should be used as primary end-points during a VE validation study.**
Results and Conclusions: **Five categories of end-points were found in the 32 scientific articles and 146 FDA reports. The most common and harmful end-points per category are: *Device Problems:* Detachment of Vacuum Extractor Cup (69%), Amount of Pulls (47%) and Time of Delivery after Application of Vacuum Extractor (38%). *Maternal Patient Problems:* Perineal Tear (82%) and Creation of Episiotomy (65%). *Neonatal Patient Problems:* Head Trauma (72%), Mortality (28%) and Apgar Score (72%). *Successful Procedure:* First Vacuum Device Success (91%). *Generic Information:* Parity (88%), Maternal Age (84%), Birth Weight (88%), Gestational Age (78%) and *Procedural Information (81%)*. Percentages refer to how often this end-point is used as an end-point in the articles.**
To the best of the author's knowledge, this is the first systematic review to provide insight into the end-points of a VE clinical validation study. When VE performance is compared with another VE in the future, it is be important to have standard and identical end-points. It is therefore scientifically relevant if these end-points are used as primary end-points in subsequent VE validation.

I. Introduction

Giving birth to a child is a complex event. When natural birth is not possible or is difficult, alternative means of facilitating delivery are often considered. Operative vaginal birth is such a procedure, consisting of the forceps method or the vacuum extraction method. Reasons for operational vaginal delivery are maternal fatigue, a non-reassuring fetal heart rate, a lengthy second stage of labour, or to reduce the second stage of labour in specific maternal circumstances [1]. In the United States, operative vaginal births account for around 1 in 20 (5%) of all deliveries [2]. Vacuum-assisted births have been on the rise, and now account for nearly four times the incidence of forceps-assisted vaginal births [3]. Advantages to use vacuum assisted delivery over forceps are that the procedure is easy to learn, results in a fast delivery, maternal discomfort is reduced, there is less genital trauma in the mother and that less anaesthesia is necessary. [1].

Vacuum extraction has been in use for a long time, since around 1705. The procedure involves extraction of the fetus using a suction cup attached to the fetal scalp. The modern era of vacuum extractors as we know them today began with the introduction of the Malmström cup in 1993 [4]. After this, several VEs were developed, such as the Bird cup and the Kobayashi cup [5], [6]. In 2001, Aldo Vacca, an obstetrician from Brisbane, came up with a new type of VE: the Kiwi OmniCup® (Clinical Innovations) [7]. Since then, the Kiwi Omnicup has been a commonly used VE around the world [8].

Fig. 1. The Kiwi OmniCup® [9]

The principle of the VE is roughly the same for all these different devices. In figure 1 you can see an image of the Kiwi

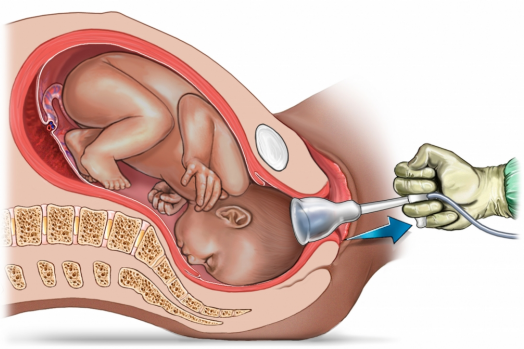

Fig. 2. Procedure of a Vacuum Extraction [10]

OmniCup®. This VE consists of a cup, which makes contact with the head of the fetus. Attached to this is a tube, through which air can flow. Furthermore, each VE has a different mechanism to create the vacuum. In the Kiwi OmniCup®, this pump mechanism can be operated with one hand. Often a VE also has a pressure gauge, to see what pressure has been achieved and whether the pressure is dropping from the cup.

The procedure of the vacuum extraction can be seen in figure 2. The obstetrician places the cup on the fetus's head, at the flexion point. The pump mechanism is then used to create the desired pressure. Traction force is applied to the vacuum cup by the obstetrician simultanious with the uterine contractions, and the baby is directed out of the birth canal. Despite the advantages of vacuum extraction, vacuum assisted delivery is also associated with a higher risk of a couple patient complications, such as perineal tears, neonatal head trauma and hemorrhage [1]. During the vacuum extraction, it is therefore of essence that the VE performs adequately and causes the least amount of complications to the mother and child.

In order to ensure optimal vacuum extractor performance, validation studies have been done to assess performance, with the goal to evaluate any benefits of the VE [11]–[13]. In such studies, various factors of the VE are assessed using a set of end-points. An end-point is an objectively measurable result that may be used to establish whether the intervention under study is effective [14]. To the best of this author's knowledge, no literature review exists that identifies the end-points of a VE validation study. This study provides a systematic review with the aim of creating a basis for a validation study of a VE. According to McLeod, it is important to establish and use clearly measurable and substantiated end-points [15]. In this review, all possible end-points are identified and categorized into primary and secondary end-points, with primary end-points being effectiveness metrics that answer the study's main objective [16], while secondary endpoints measure additional effects [17]. In this review, primary end-points are selected based on their incidence and harmfulness. This will ultimately result in well-founded advice for primary end-points that should be used during the validation of a VE. Ultimately, the following research question can be answered: *What are the relevant primary end-points for a validation study of a vacuum extractor?*

II. Methods

This section will explain the methods of this review. The analysis was done using two different approaches. First, scientific articles were sought in the SCOPUS and MEDLINE databases. In this search, articles were included in which a vacuum extractor was validated. The search terms and inclusion strategy will be explained later. Furthermore, the database of the U.S. Food and Drug Administration (FDA) was searched for complications and problems related to the vacuum extractor. In this way, vacuum extraction is looked at from two different angles: from the scientific angle and from the complications encountered during the use of different vacuum extractors in real life. In the scientific articles and the FDA complications, a distinction was made between *Device Problems* and *Patient Problems*. Furthermore, in the scientific articles, end-points were divided into the following additional categories: *Successful Procedure, Clinical & Patient Experience* and *Generic Information*. A simplified overview of the two methods is given in Figure 3.

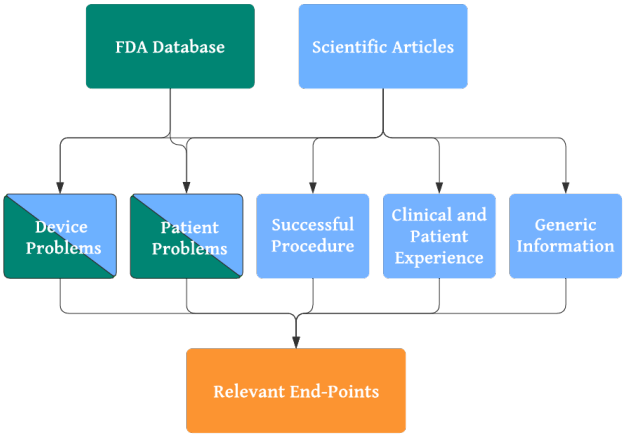

Fig. 3. Flowchart of used method

For this literature review, it was decided to use the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method. The PRISMA method will be used by following the guidelines for a systematic review as described in the article by Liberati, et al. (2009) [18].

A. Scientific Articles

1) Search Strategy: The first method was to search for scientific articles validating vacuum extractors. The databases used for finding the validation studies of vacuum extractors were MEDLINE and SCOPUS. These are two large bibliographic databases in which medical studies are well represented. First, sufficient search terms were drawn up. These search terms were twofold. First, terms and synonyms

TABLE I
SEARCH TERMS FOR SCIENTIFIC ARTICLES

Database	**Vacuum Extraction**	**Validation Study***	**Excluded Terms in Title**
SCOPUS	Vacuum Extractor/Extraction Kiwi Cup Omnicup Ventouse Vacuum Assisted Deliveries	Clinical Trial/Evaluation Validation Comparison Efficacy Observational Study	-
MEDLINE	Vacuum Extractor/Extraction Kiwi Omnicup Ventouse Vacuum Pump Vacuum Assisted Deliveries	Clinical Trial Efficacy Observational Study	Forceps Cesarean Wound Therapy

* SCOPUS and MEDLINE terms may differ because of irrelevance for search outcome

describing a vacuum extractor were defined. Secondly, terms describing a clinical trial or validation study were included. Both the terms describing vacuum extraction and clinical trial terms were a requirement in the search strategy. This was achieved by accurately using the "AND" and "OR" functions in the advanced search function of the databases. Furthermore, the filter was set to show only articles from the year 2000 onward. After entering the original terms in MEDLINE and SCOPUS, a number of results followed. This was followed by an iterative process in which the terms were continually adjusted on the basis of important articles found. After the first searches, multiple articles were found in which vacuum extractors were compared with forceps and caesarean sections. By reading those articles, it was seen that the research designs were not relevant for this literature review, because the chosen end-points were very diverse because the vacuum extractor was not the only focus. Eventually, the search terms became more specific and more relevant articles were found. In table I, the search terms for both SCOPUS and MEDLINE can be found. Furthermore, the table of final search strings can be found in Appendix A. The final results of the advanced search in MEDLINE and SCOPUS were exported to the reference manager, Mendeley. The duplicates were removed in Mendeley.

2) Eligibility Criteria: The remaining articles from the searches in MEDLINE and SCOPUS were screened and further examined. First, the title and abstract of each article were read. The titles and abstracts had to meet a number of criteria:

- Studies must aim to validate a vacuum extractor:
  - Compare a vacuum extractor with another VE
  - Validate a vacuum extractor with no control group** **These studies are very similar to the comparison studies with another VE
  - Comparison of a VE with caesarean section or forceps was **not** included
- Studies must be a human clinical trial
- Studies need to be performed since the year 2000
- Studies must be written in English and a full text must be available

Once the titles and abstracts were read and articles were excluded, the full text of the articles was read. Based on the reading of the full texts, articles were again excluded from the systematic review based on the following criteria:

- Studies must have clear end-points stated in the full text
- Studies must be clearly documented and repeatable
- Studies were **not** included if only one specific end-point was investigated

In the end, a number of articles remained that were included in the analysis of this systematic review.

3) Data Extraction: The articles were manually exported from Mendeley Reference Manager to Google Sheets in Google Drive. The data was manually sorted by title, authors, link to full text and end-points. The end-points were subdivided into subcategories, more on this in the data interpretation.

4) Data Interpretation and Analysis: Once the articles were in Google Sheets, the data could be interpreted, starting with the subdivision of the end-points. Different categories were created:

- **Device Problems:** These are the end-points that measure aspects of the device, such as break or detachment of the cup.
- **Patient Problems:** These are the end-points that monitor the complications of the patients. A distinction was made between maternal complications and neonatal complications.
- **Successful Procedure:** These are the end-points that measure the overall success of the VE procedure.
- **Clinical and Patient Experience:** These are the end-points that measure the experience and satisfaction of both the patient and the clinical end-user.
- **Generic Information:** These 'end-points' are about the general information that was collected before, during or

after each study. This regarded the information that had nothing to do with the device, but about the background information of the end user, mother and child, among others.

From each full text of the articles included, it was counted how often which end-points were used in each study, and this was documented in a table. Next, the total number of times this end-point was measured was counted. If applicable, certain end-points were categorized. After this, a percentage was calculated for each end-point to give an insight into how relevant this end-point is in validation studies of vacuum extractors. This calculation went as follows for each end-point:

$$\%\ \text{endpoint} = \frac{\#\ \text{endpoint used in studies}}{\#\ \text{studies}} * 100\%$$

Ultimately, graphs were created showing the percentage incidence of the end-points found in the literature. These percentages show how often the end-points are used in scientific articles.

B. Complications Database FDA

1) Search Strategy: As mentioned earlier, the search for relevant end-points for a validation study of a vacuum extractor consisted of two methods. In the second method, a different approach was used than in the first method, namely the search in the medical devices database of the U.S. Food and Drug Administration (FDA). In this Total Product Life Cycle (TPLC) database, problems with various medical devices are reported. A vacuum extractor was used in the search string of the database and the data from 'Extractor, Vacuum, Fetal' was chosen to be included in this review. The data range was set for problems with the vacuum extractor from the year 2007 onwards, because this is the year that the FDA reports start in the database. The device problems and patient problems were separated and then automatically displayed in a Microsoft Excel document. Data was sorted by report number, event date, event type, manufacturer of vacuum extractor, product code, brand name, patient problem(s), device problem(s) and event text.

2) Eligibility Criteria: In order for the complication reports to be included in this systematic review, they needed to fulfil certain criteria. First, the event texts of all reports were read thoroughly. Event texts were excluded if it was not clear which device problems were involved. The device end-points were only assigned if they actually caused a problem in the procedure. Furthermore, the following device problems were not included in this review due to their irrelevance: *Adverse Event Without Identified Device or Use Problem, Appropriate Term/Code Not Available* and *Insufficient Information*. Additionally, the following patient problems were also not included: *No Known Impact Or Consequence To Patient, No Consequences Or Impact To Patient, No Information, Insufficient Information, No Code Available, No Clinical Signs, Symptoms or Conditions, No Patient Involvement* and *Appropriate Clinical Signs, Symptoms, Conditions Term/Code Not Available*.

3) Data interpretation: Similar to the data of the scientific articles, the FDA data were interpreted in different ways. A distinction was made between the following types of data:

- **Device Problems:** These are the end-points that measure aspects of the device or about the procedure of the device/method.
- **Patient Problems:** These are the end-points that measure the complications of the patients. A distinction was made between maternal complications and neonatal complications.

a) Interpretation of Patient Problems: For the interpretation of the patient problems found in the FDA database, a different method was used than for the interpretation of the patient problems found in the literature. To begin with, the incidence of patient problems occurring in the FDA reports was counted. The number of patient problem end-points appearing in the reports were counted using the "COUNT-IF" function from the Excel file. Subcategories of the end-points were also created and plotted.

In order to interpret the relevance of the patient problems and complications, not only the frequency of occurrence of a patient problem was examined, but also the severity of the complications. In this way, a more informed choice of patient problems end-points could be made. The severity was determined by using the Clavien Dindo classification, first introduced by Dindo et al. in 2004 [19]. This classification aims to create a scale of severity in complications. The scale is classified according to the following grades:

- Grade I: Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions.
- Grade II: Requiring pharmacological treatment with drugs other than such allowed for grade I complications.
- Grade III: Requiring surgical, endoscopic or radiological intervention.
- Grade IV: Life-threatening complication (including central nervous system complications) requiring IC/ICU management.
- Grade V: Death of a patient. [19]

In this systematic review, each patient problem found in the FDA reports has been assigned a severity level according to the Clavien-Dindo classification. By looking at the incidence and severity, an overall Score of Harmfulness (SoH) of the relevance of each patient problem was created. This was done using the following formula:

$$\text{SoH} = \text{endpoint in FDA reports} * \text{ClavienDindo score}$$

b) Interpretation of Device Problems: For the interpretation of the device problems, another method was used. First, device problems were counted in the FDA reports using the "COUNT-IF" function in Excel. From the total list of device end-points found, some end-points were merged to form device problem categories, because they essentially meant the same thing or were synonyms. In the FDA reports,

both a problem is reported for the patient as for the device. This means that all device problems lead to certain patient problems. So, in order to determine the relevance of a device end-point, the linked patient problems and the corresponding Clavien-Dindo scores were looked at. For every time a device problem was reported, the patient-problems were noted, same for the Clavien-Dindo scores. The Clavien-Dindo scores of the patient problems can be found in Appendix B. If the patient problems were any of the following: *No Known Impact Or Consequence To Patient, No Consequences Or Impact To Patient, No Information, Insufficient Information, No Code Available, No Clinical Signs, Symptoms or Conditions, No Patient Involvement* and *Appropriate Clinical Signs, Symptoms, Conditions Term/Code Not Available*, a Clavien-Dindo score of 1 was given. This is done to indicate that a device problem occurred. Even tough no 'real' patient problem occurred, there was still a problem with the device.

All the Clavien-Dindo scores were added together to form the total Clavien-Dindo score for each device category. Those total scores were plotted for each device end-point found in the FDA reports. Furthermore, a table was created in which the device end-points from the FDA reports were linked to the device end-points of the scientific literature, in order to give more insight to the relevance of the end-points.

III. Results

A. Scientific Literature

1) Search Results: On 30 March 2022, the search strings, found in Appendix A, were entered in SCOPUS and MEDLINE. In SCOPUS 96 articles were found, and in MEDLINE 211 articles were found. Thus, a total of 307 articles were identified by both data sources. Of this total, a number (n=6) did not have a full text available, leaving 301 articles. After removing the duplicates (n=18) in Mendeley, 283 articles remained. After reading the titles and abstracts and applying the eligibility criteria set out in the method, articles were again removed (n=234) from the analysis. Most articles were removed because they compared a vacuum extractor with the forceps or caesarean section. This left 49 articles. By searching for similar articles in MEDLINE of 2 key articles [20], [21], additional articles (n=16) were added. In total, the full text of 65 articles was read. Based on the full text eligibility criteria, 33 articles were excluded from the analysis. In the end, 32 articles were included in this systematic review. The PRISMA flow chart [18], [22] of these results can be found in figure 4.

2) Analysis:

a) Device Problems: In the 32 studies that were included in this review, 4 different device end-points were found: *Detachment of Cup* (n=22), *Amount of Pulls* (n=15), *Time of Delivery after Cup Application* (n=12) and *Maximum Traction Force* (n=5). For each device end-point, the incidence is shown as a percentage of the total of numbers of studies, according to the formula introduced in the method. This overview can be seen in Figure 5.

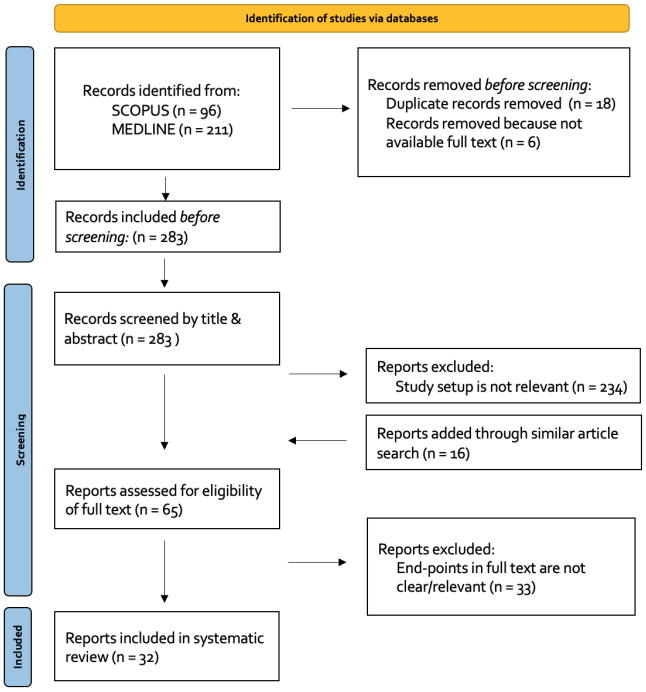

Fig. 4. The flowchart of the PRISMA method used in this review

b) Patient Problems: Besides device problems, end-points were also found that measured patient problems/complications during the validation study. These patient problems have been divided into two categories: Maternal Complications and Neonatal Complications. In the studies, 9 end-points were found for maternal complications and 23 end-points for neonatal complications. The definitions of these end-points can be found in Appendix E. Figure 6 and Figure 7 give an overview of the incidence of these end-points in all articles.

c) Successful Procedure: In the studies that were selected for this review, 4 successful procedure end-points were found. For each independent device end-point, the incidence is shown as a percentage of the total of numbers of studies, according to the formula introduced in the method, depicted in Figure 8. The percentage thus means to what extent this procedural problem is used as an end-point in the studies.

d) Generic Information: The 32 studies were also examined for the generic information. From these studies, 19 'end-points' were found, which were noted before or during the delivery. These end-points can be divided into three categories: *Maternal Information*, *Neonatal Information* and *Procedural Information*. The percentage incidence of the generic information can be seen in Figure 10.

B. FDA Database

1) Search Results: To gain insight into patient complications during real deliveries, a data search was performed in the FDA's TPLC database. On 30 April 2022, the final search was done for 'extractor, vacuum, fetal'. This search resulted in 146 Medical Device Reporting (MDR) reports. In these MDR

reports, both device problems (n=54) and patient problems (n=47) were found. After removing the irrelevant device and patient problems, as described in the criteria in the method, 51 and 25 device and patient problems respectively remained. The definitions of each end-point can be found in Appendix F. These problems were included in the analysis of this systemic review.

2) Analysis:

a) Device Problems: As discussed, a total of 51 eligible different types of device problems were found in the 146 reports. In order to create a better overview of the complications, categories have again been created. These device problems are divided into the following six categories: *Suction Problem/Detachment of Cup*, *Break of Device*, *Incorrect Procedure*, *Deflation Problem*, *Entrapment of Device* and *Pumping Problem*. An elaborate, detailed definition of these categories can be found in Appendix F. As discussed in the method, each report was looked at to see which device problem leads to which patient problem. Then the Clavien-Dindo scores of those same patient problems were added together. In the end, each device problem from the FDA database got a total score of the Clavien-Dindo scores added together. In Table IV in Appendix B it can be seen which patient problems with corresponding score are linked to the device problems. The total Clavien-Dindo score for the categories is as follows: *Suction Problem/Detachment of Cup* = 128, *Break of Device* = 99, *Deflation Problem* = 14, *Incorrect Procedure* = 52, *Entrapment of Device* = 3 and *Pumping Problem* = 3. Furthermore, in Figure 11, it can be seen per device end-point category what this total Clavien-Dindo score is, which gives an indication of the relevance of each device end-point found in the FDA database.

b) Patient Problems: As mentioned, 25 eligible patient problems were found in the FDA database. These are both maternal (n = 4) and neonatal (n = 21) complications. Figure 13 in Appendix C shows the incidence of these patient problems. Furthermore, the Clavien-Dindo classifications of these patient problems are shown in Table IV in Appendix B. Below, in Figure 12, the score of harmfulness is shown for each patient end-point. This figure shows the relevance of each patient end-point found in the FDA database.

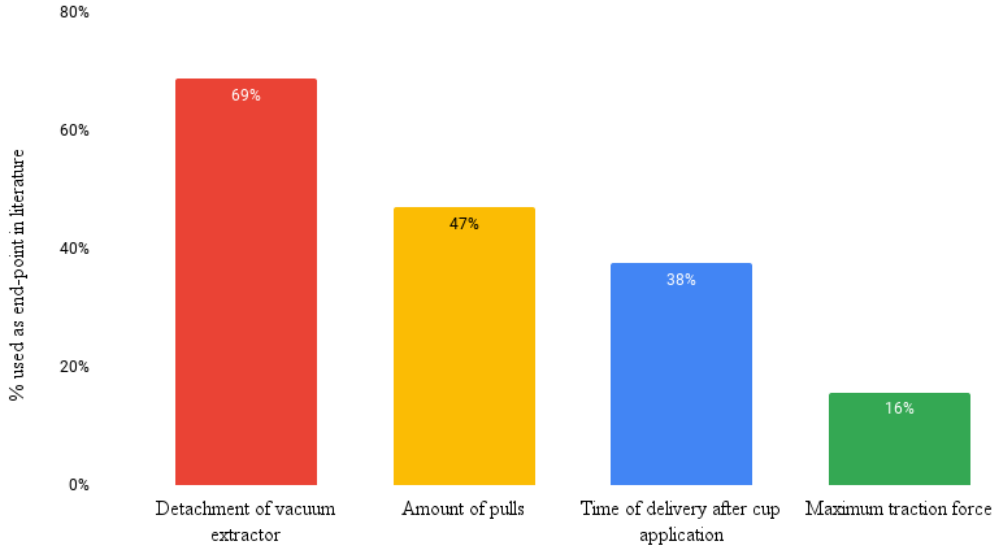

Fig. 5. The percentage incidence of the *Device Problems* end-points found in the literature

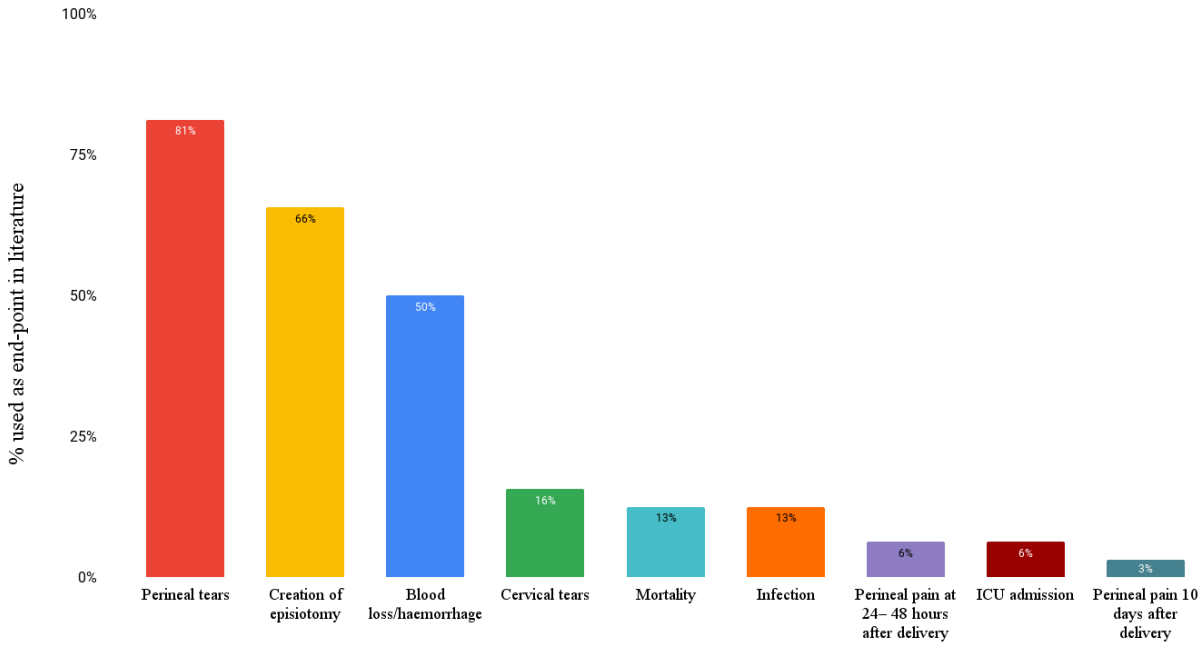

Fig. 6. The percentage incidence of the *Maternal Patient Problems* end-points found in the literature

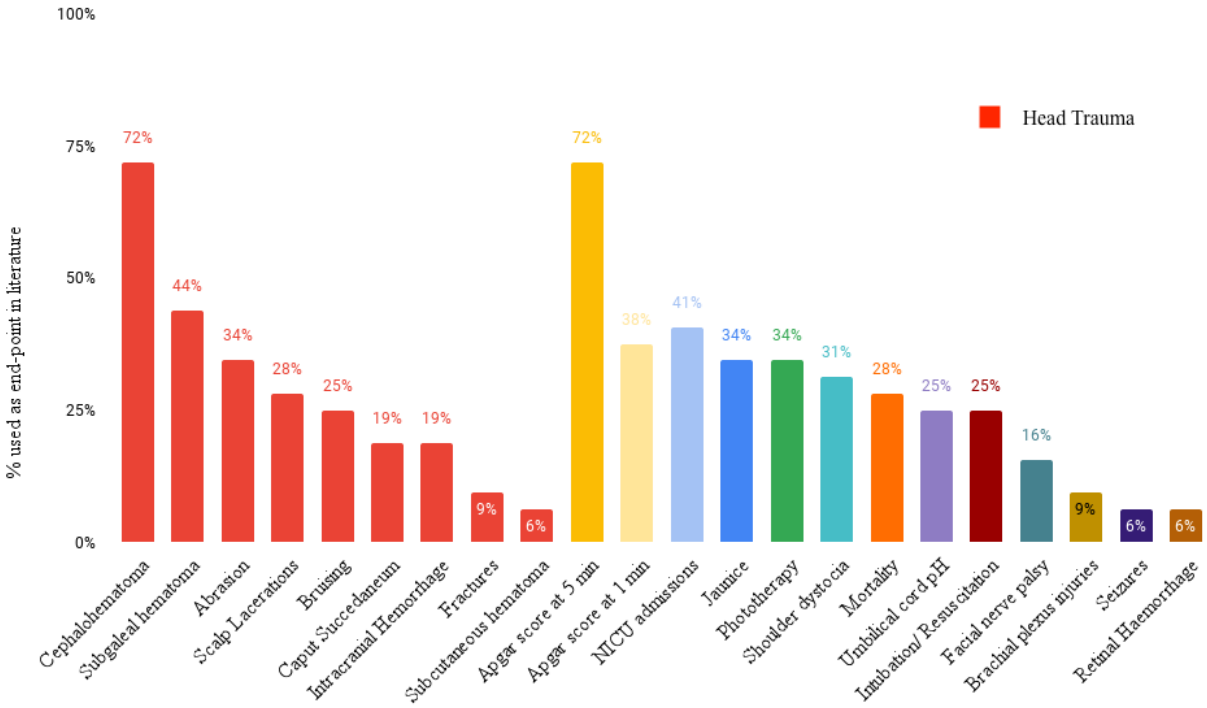

Fig. 7. The percentage incidence of the *Neonatal Patient Problems* end-points found in the literature

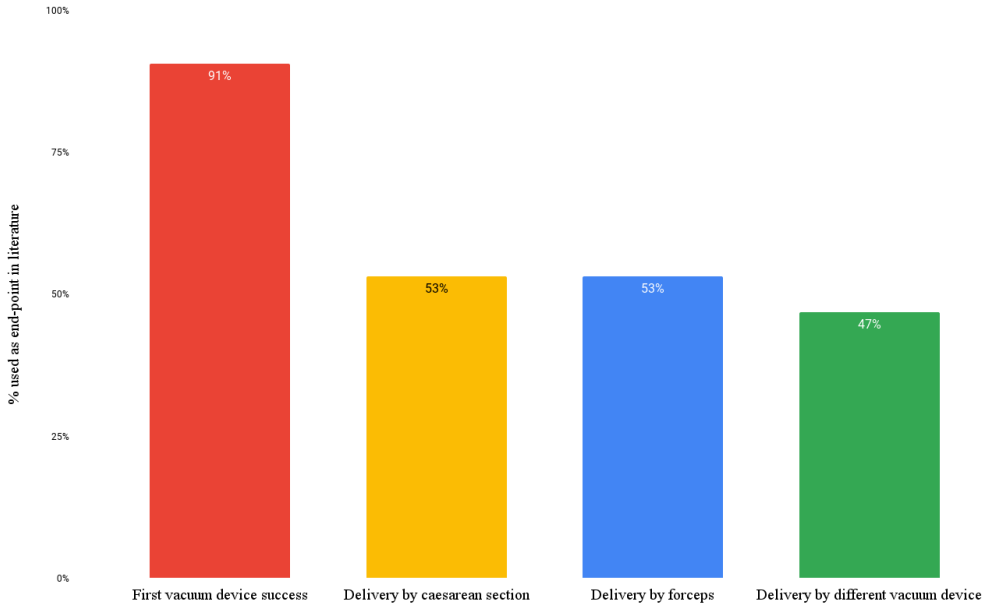

Fig. 8. The percentage incidence of the *Successful Procedure* end-points found in the literature

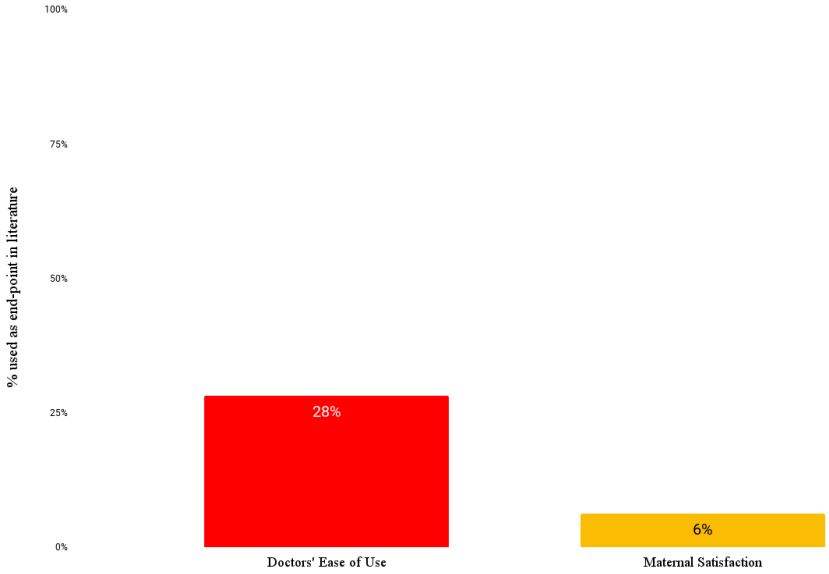

Fig. 9. The percentage incidence of the *Clinical and Patient Experience* end-points found in the literature

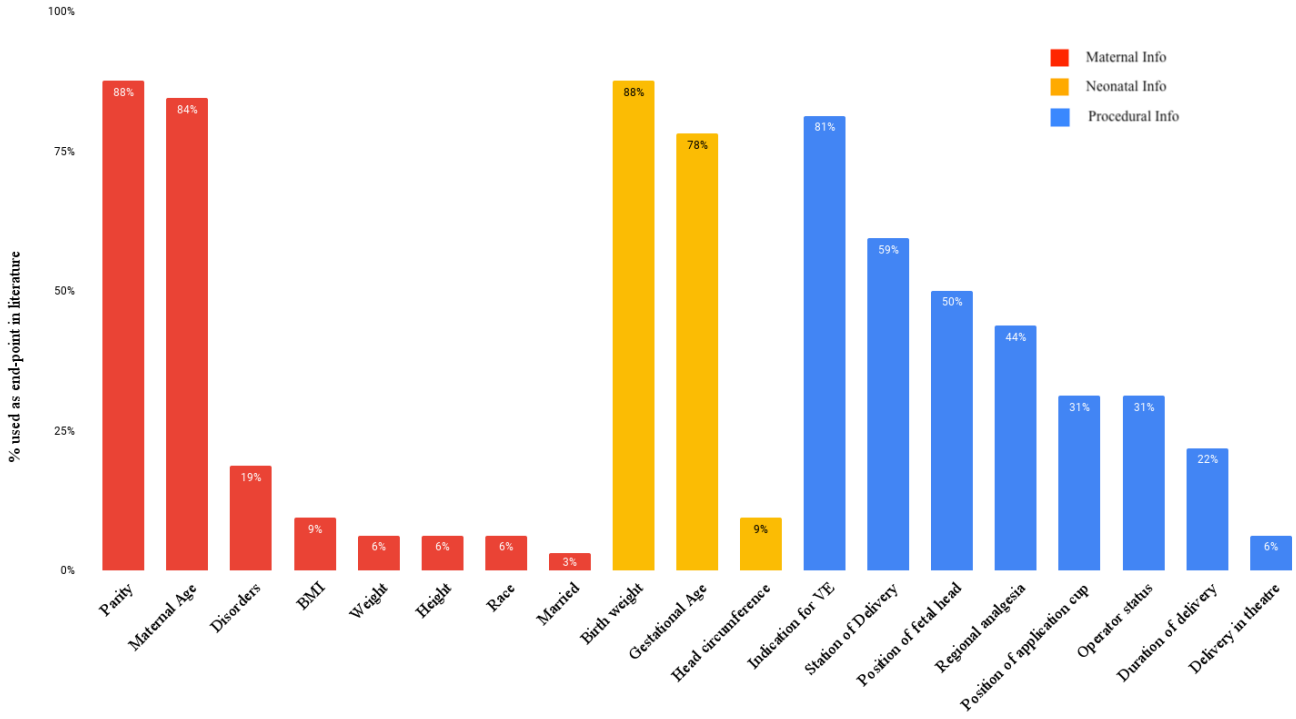

Fig. 10. The percentage incidence of the *Generic Information* end-points found in the literature

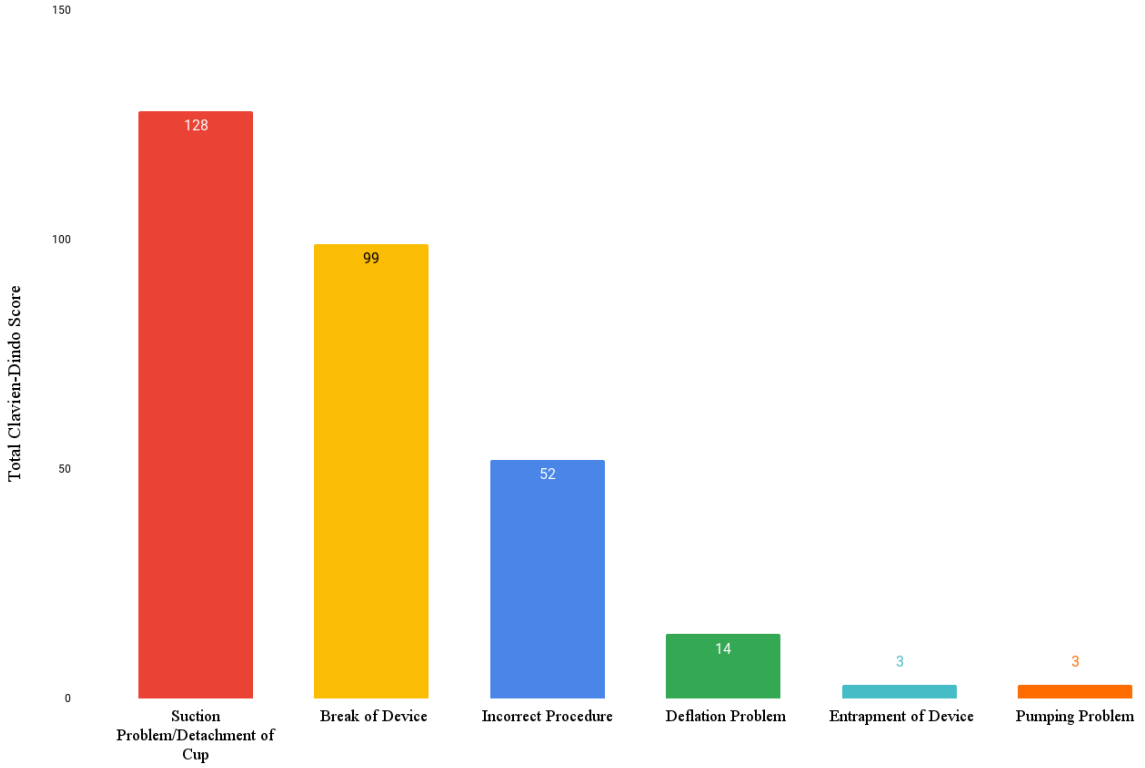

Fig. 11. The total Clavien-Dindo score of each device end-point found in the FDA reports

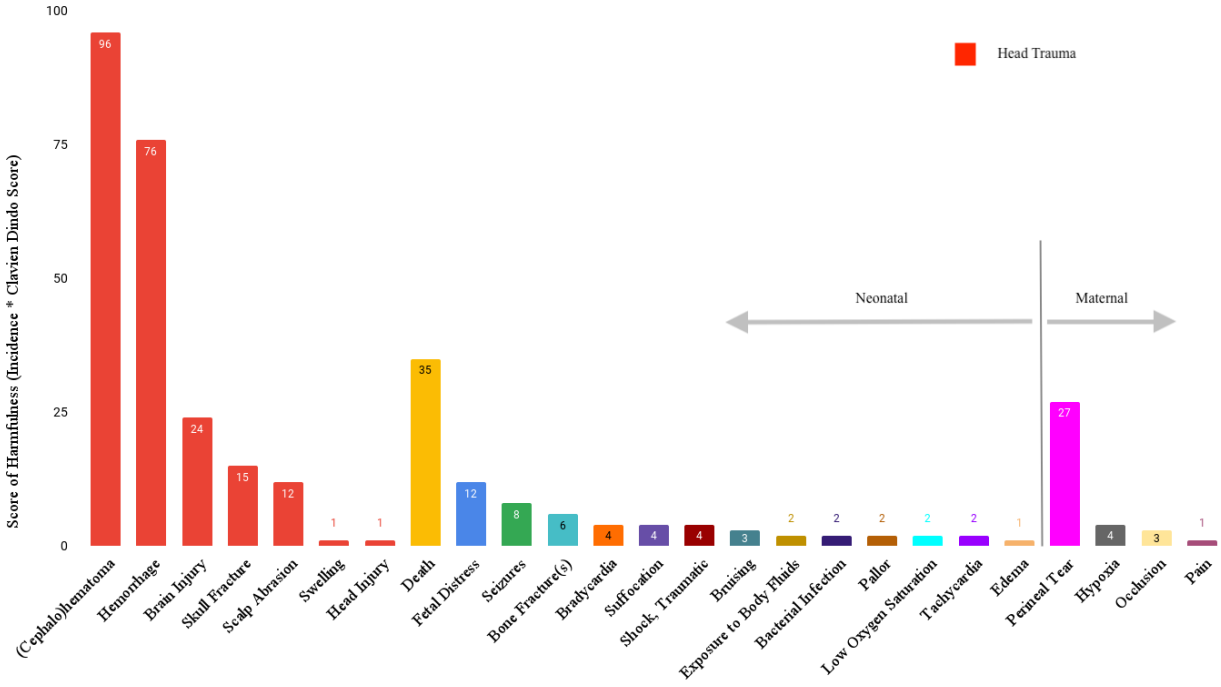

Fig. 12. Score of Harmfulness for each patient end-point found in the FDA reports

TABLE II
LINK BETWEEN DEVICE PROBLEMS FROM THE LITERATURE AND FDA REPORTS

FDA / **Literature**		Suction Problem	Break of Device	Incorrect Procedure	Deflation Problem	Entrapment of Device	Pumping Problem
	Total C-D / **Incidence**	*128*	*99*	*52*	*14*	*3*	*3*
Detachment of VE cup	*69%*	x	x	x			
Amount of pulls	*47%*			x			
Time of delivery after VE application	*38%*	x	x	x	x		
Maximum traction force	*16%*			x		x	

IV. Discussion

From the results found in the scientific literature and the FDA reports, 5 different categories of end-points were found, namely: *Device Problems, Patient Problems (Maternal/Neonatal), Successful Procedure, Clinical & Patient Experience* and *Generic Information*. Next to the insight in these categories, a recommendation about the individual end-points in terms of relevance will be given in this part. Eventually, a conclusion can be drawn whether each end-point should be used as primary end-point.

A. Relevance of End-Points

This review was conducted with the goal to give an insight in the end-points used in a clinical validation of a vacuum extractor. Based on the incidence in both the scientific literature and the FDA reports, a substantiated recommendation will be given which end-point are most relevant and should be used as primary end-points in a validation study. However, the more secondary end-point used in a study, the more correlations can be established, and more insights can be found [15]. This systematic review is, to the knowledge of this author, the first review to give an insight in the most relevant end-points during a vacuum extractor validation. That is why the recommendation below gives an overview of the most important primary end-points, but all the end-points (and their incidence) that are mentioned in this review are a relevant tool for the preparation of a vacuum extractor validation.

1) Device End-Points: In order to be able to make a well-considered choice of device end-points, it is important to not only look at the literature, but also at the FDA reports. This way, a well-founded insight can be given into the most important and relevant end-points during a clinical study for validating a vacuum extractor. Furthermore, the analysis in this review of the device problems in the FDA reports took into account the severity of the patient problems linked to these device problems [19]. In order to link the device problems of both databases to each other, Table II was created in the results. For each device end-point from the literature, this table shows which device end-point from the FDA reports corresponds best with it. If these end-points correspond, this is indicated by a cross. This cross, together with the incidence and total Clavien-Dindo score per end-point, will determine the relevance. This table will be used to make conclusions per device end-point. The relevant primary end-points for a clinical validation study of a vacuum extractor device are listed below:

- **Detachment of Vacuum Extractor Cup**
  The end-point *Detachment of Vacuum Extractor Cup* is used in 22 of 32 scientific articles (69%). Based on the incidence alone, this would be a relevant primary end-point. Furthermore, in Table II, this end-point resembles most with the device problem of *Suction Problem/Detachment of Cup*, which has a total Clavien-Dindo score of 128, which is the highest score of all device problems reported in the FDA reports. Moreover, a study of Krispin et al. (2017) acknowledges the correlation between cup detachment and neonatal head trauma, suggesting the relevance of this end-point [23]. Because of the high incidence in literature and high Clavien-Dindo score, the device problem *Detachment of Vacuum Extractor Cup* is recommended to use as a primary device end-point in a clinical validation study of a vacuum extractor.
- **Amount of Pulls**
  The end-point *Amount of Pulls* is used in 15 of the 32 of the scientific articles (47%). This device problem is also linked to the device problem *Incorrect Procedure*, which has a total Clavien-Dindo score of 52. Furthermore, the *Amount of Pulls* is an important end-point, because four or more pulls with a vacuum extractor can lead to a serious increase in risk of NICU admission [24]. If you want to validate a vacuum extractor, it is therefore important that the amount of pulls to deliver a baby has a maximum of three pulls. That is why *Amount of Pulls* is recommended as a primary device end-point for vacuum extractor validation study.
- **Time of Delivery after Application of Vacuum Extractor**
  The device end-point *Time of Delivery after Application Vacuum Extractor* is used in 12 of the 32 scientific articles (38%). This indicates that this might be a reasonable relevant end-point. Additionally, as can be seen in Table II, this end-point resembles the following end-point found in the FDA reports: *Suction Problem/Detachment of Cup, Break of Device, Incorrect Procedure Entrapment*, with a total Clavien-Dindo score of 128, 99, 52 and 3, respectively. These scores added together, a score of 282 results. This indicates that the end-point Time of Delivery after Application of Vacuum Extractor is important to measure during a vacuum extractor validation. Furthermore, in a study of Mollberg et al. (2005), the conclusion is drawn that duration of vacuum extraction is a direct risk factor for brachial plexus palsy, which has a Clavien-Dindo score of 3 [25]. Because of this, the incidence in the literature and the correspondence with 4 device end-points from FDA reports, the end-point *Time of Delivery after Application Vacuum Extractor* is also proposed as a relevant primary device end-point.

Furthermore, the other three device problems found in the FDA reports with the highest total Clavien-Dindo score (*Suction Problem/Detachment of Cup, Break of Device, Incorrect Procedure*) are indirectly incorporated in these recommended three end-points above, because of the correspondence in Table II. That is why they are not recommended as separate primary end-points.

2) Patient End-Points: Similar to the device end-points, it is also important for patient end-points to look at both the scientific literature and the FDA reports. If a patient problem is used in both the literature and the FDA reports, it is preferred to be used as a primary end-point. Furthermore,

patient end-points are also considered relevant if they have a high percentage incidence in the literature or a high score of harmfulness. The following both maternal and neonatal patient end-points are considered most relevant for a clinical validation study of a vacuum extractor:

a) Maternal End-Points:

- **Perineal Tear**
  The end-point *Perineal Tear* is used as end-point in 26 of 32 scientific articles (82%). Furthermore, this is the maternal patient end-point with the highest score of harmfulness (=27). In a study of Kreft et al. (2020), the conclusion is also drawn that there were significant more vaginal tears when using a vacuum extractor than in spontaneous births [26]. On the other hand, there are numerous risk factors for perineal tears, such as parity and prolonged stage of labour [27]. When drawing conclusions about the correlation between a vacuum extractor and perineal tears, it is of great importance to take into account all these risk factors and to be cautious when making assumptions. Nevertheless, this end-point is recommended to use as a primary end-point.
- **Creation of Episiotomy**
  This end-point is used as end-point in 21 of 32 articles (65%). However, this end-point is never reported in the FDA as a maternal patient problem. An episiotomy is performed by the clinician in order to maximize the success of the vacuum extraction, for instance to make the cup fit properly [28]. Furthermore, episiotomies are often performed with the goal of preventing perineal tears. That is why this 'choice of the clinician' is not seen as a patient complication in the FDA reports. Nevertheless, this is a relevant end-point during a validation of a vacuum extractor, because it is interlinked with perineal tears and can say a lot about the correlation between VE performance and perineal tear. Also because of the incidence in the scientific articles, the end-point *Creation of Episiotomy* is recommended as a primary end-point to use in a validation study.

b) Neonatal End-Points:

- **Category Head Trauma**
  In the scientific literature, neonatal head trauma is the category that is used most as an end-point. There are 9 end-points found that measure neonatal head trauma. The end-points *Cephalohematoma, Subgaleal Hematoma, Abrasion, Scalp Lacerations* and *Bruising* have the highest percentage incidence, namely 72%, 44%, 34%, 28% and 25%, respectively. Moreover, in the FDA reports, the category neonatal head trauma also scores the highest score of harmfulness. The individual end-points that receive the highest score of harmfulness are *(Cephalo)hematoma, Hemorrhage* and *Brain Injury*, with a score of 96, 76 and 24, respectively. To proof support for these results, there are numerous articles that underpin the harmfulness of vacuum extraction in terms of head trauma [29] [30] [31]. In all of these studies, head trauma can cause permanent damage for neonates. Therefore, it is important that during the validation of a vacuum extractor, it is confirmed that the vacuum extractor causes the least possible neonatal head trauma. In terms of this systematic review, all the neonatal patient end-points found in the literature and the FDA will be recommended to use as primary end-points in a validation study of a vacuum extractor.
- **Mortality**
  In both the literature, as the FDA reports, neonatal mortality was an overarching end-point. The incidence in the literature was 9 out of 32 articles (28%). The score of harmfulness was 35, ending in the top three of patient end-points found in the FDA reports. During a vacuum extraction, the risk of mortality is generally increased, compared to natural birth [32]. However, it is important to verify if this increased risk is the direct result of the vacuum extractor, or if the delivery has become complicated due to other factors such as the indicators, due to which it was decided to perform vacuum extraction. However, because of its incidence and score of harmfulness, the neonatal patient end-point *Mortality* is a recommended primary end-point.
- **Apgar Score**
  The end-points *Apgar score at 5 min* and *Apgar score at 1 min* are used as end-point in respectively 72% and 38% of the articles. The Apgar score is a frequently used method for evaluating neonatals, and it is an important parameter when conducting a study with neonatals [33]. However, the Apgar score can be influenced by a lot of different factors other than the effects of vacuum extraction [34]. Because of its incidence and relevance, it is important to use the *Apgar Score* as a primary end-point in a vacuum extractor validation study, but drawing the conclusion of correlation between Apgar score and vacuum extraction should be done with caution.

Furthermore, if a patient problem is reported in the FDA reports, this means that this patient problem has occurred during an actual vacuum extraction and this patient problem is of significance. That is why all patient problems reported in the FDA database are recommended as secondary end-points, and these are proposed to be taken into account during a vacuum extraction validation study. These are the following patient end-points: *Neonatal: Fetal Distress, Seizures, Bone Fracture(s), Bradycardia, Suffocation, Traumatic Shock, Bruising, Exposure to Body Fluids, Bacterial Infection, Pallor, Low Oxygen Saturation, Tachycardia*, *Edema* and *Maternal: Hypoxia, Occlusion* and *Pain*.

3) Successful Procedure: The *Successful Procedure* end-points were found in the scientific literature. The following end-points in this category were found in the literature: *First Vacuum Device Success, Delivery by Caesarean Section, Delivery by Forceps* and *Delivery by Different Vacuum*

Device, with an end-point incidence of 91, 53, 53 and 47% respectively. The end-point *First Vacuum Device Success* is therefore a relevant primary end-point, because it gives insight in whether the vacuum extractor does its work, independent of the complications.

4) Clinical and Patient Experience: The end-points that fall into this category were also found in the scientific literature, and are as follows: *Doctors' Ease of Use* and *Maternal Satisfaction*, with incidence of 28% and 6% respectively. This means that these categories are not regarded of much importance during a clinical validation. These end-point would for instance have more significance during a general validation, before a real clinical trial. That is why, in this review, the end-points *Doctors' Ease of Use* and *Maternal Satisfaction* are recommended as secondary end-points.

5) Generic End-Points: As discussed in the method, these are the 'end-points' that are measured before, during or after the delivery that are not dependent on the vacuum extractor. However, it can be important to report this information, when drawing conclusions about correlations. The most important generic end-points are listed below.

a) Maternal Information:

- **Parity**
  This end-point is used in 28 of 32 scientific articles (88%), which is the maternal generic end-point with the highest incidence. Furthermore, primiparity is associated with higher patient complications risk during vacuum assisted delivery [35]. That is why it is recommended to take down the parity of the mother during a validation study of a vacuum extractor.
- **Maternal Age**
  The end-point *Maternal Age* was used in 27 of 32 articles (84%). Furthermore, in a study of Aiken et al. (2014), a correlation is found between vacuum extraction success and maternal age [36]. Therefore, it is important to note the *Maternal Age* during a validation study.

b) Neonatal Information:

- **Birth Weight**
  This end-point is used in 28 of 32 articles (88%). However, several studies conclude that birth weight is no indicator for complicated or non-successful vacuum extraction [37] [38]. Nevertheless, because of the incidence in the literature, it is still important to note this end-point during a validation study. This end-point may have no influence on the outcome of the study, but it is still important to verify the influence and possible correlation.
- **Gestational Age**
  The end-point *Gestational Age* occurs in 25 of 32 articles (78%). In other literature, the expert recommendation is made that the gestational age should not be less than 34 weeks when performing a vacuum extraction, otherwise there is a significant higher risk for neonatal trauma [39]. That is why it is important to keep track of the gestational age, in order to draw no insufficient conclusions in a validation study of a vacuum extractor.

c) Procedural Information: The following procedural generic end-points had the highest incidence in the scientific literature: *Indication for VE, Position of Fetal Head, Regional Analgesia, Position of Application Cup, Station of Delivery* and *Operator Status* with a respective incidence of 81, 59, 50, 44, 31, 31%. Various literature supports the relevance of these end-points [40] [1] [41]. That's why all these procedural generic end-points are recommended.

B. Limitations

This systemic review provides an insight into the end-points used in a clinical validation study of a vacuum extractor. Based on the incidence, the score of harmfulness and additional literature, a recommendation is made for primary end-points. However, in drawing these conclusions, there are several limitations to this systematic review that may have influenced its results. These limitations are discussed below.

1) Scientific Articles: During the search for scientific articles, the SCOPUS and MEDLINE databases were used. During the formulation of the search terms, various terms were included and excluded. Due to the human choice of search terms, important articles may have been excluded by chance. Furthermore, of the 283 articles found, only 32 articles remained after screening for eligibility criteria. These eligibility criteria were applied after reading the full texts of the articles, which may result in human interpretation errors. Moreover, some end-points were not well-defined in the articles, which meant that they were possibly misinterpreted and included in the wrong end-point category. Also, the interpretations were made by one reader, namely the author of this review. This has caused a chance of bias from the reader, which lowers the accuracy of the review. What is more, 32 articles can be interpreted as a low number of articles, which may have lowered the accuracy of the results and conclusions of this systematic review. Besides, this review only included articles that compared one vacuum extractor with another vacuum extractor or articles that had no control group. This was done because the end-points would then be the most similar, but a more complete systematic review would probably also include articles comparing a vacuum extractor with forceps or cesaerean section. Additionally, conclusions are drawn largely based on this scientific literature. Possibly there can be a bias here because only peer review papers are thus included, which leaves out the grey literature: this has possibly altered the results. Lastly, all individual articles were regarded as equally relevant in this review, although the quality of the articles varied in some cases. Preferably, a quality assessment index could bring more substantiation to this review. However, because of the already small amount of articles included in this review, the decision was made not to exclude any more articles.

2) FDA Reports: During the selection of reported incidents with a vacuum extractor, only the TPLC database of the FDA was used, which covers only the incidents in the United States of America. There may be other types of reported incidents in other countries, which could have changed the results. The other databases of other countries were private and this author was not able to gain insight in them. Furthermore, a total of 146 MDR reports were found from the year 2007 till 2022 in the FDA database. In an article of Gopalani et al. (2005), the prediction is made that incidents related to vacuum extraction are often under-reported to the FDA [42]. In addition, incidents are frequently only reported if a severe complication occurs, such as mortality of mother or child. This causes that minor incidents are potentially not reported and therefore not taken into account in this systemic review. In line with the scientific literature, the event texts were read and interpreted by one reader, and thus bias from this reader is a limitation in this review. This may have caused misinterpretation between device and patient problems. Because the Clavien-Dindo scores for device end-points were given based upon these scores, this may have limited and altered the results. Moreover, the Clavien-Dindo scores were also given to the patient problems based on the interpretation of this author. Although the guidelines for the Clavien-Dindo scores are clear, some patient problems could be classified into two categories. Furthermore, from the long list of device and patient problems in the FDA reports, subcategories were made, which were designed and filled by this author, again suggesting potential misinterpretation.

V. Conclusion

The purpose of this systematic literature review was to provide insight into end-points used during a clinical validation study of a vacuum extractor and to additionally make a recommendation as to which endpoints are the most relevant and should therefore be used as primary endpoints during such a validation study. To the best of this author's knowledge, this is the first systematic literature review to provide insight into the relevant endpoints used in a clinical study to validate a vacuum extractor. In the interpretation of the results, the relevance of each individual end-point was based on two aspects: the number of times the end-point was used in scientific articles over the past 22 years, and the score of harmfulness in FDA reports of incidents with vacuum extractors since 2007. The most relevant end-points recommended as primary end-points, divided into their categories, are: ***Device Problems:*** *Detachment of Vacuum Extractor Cup, Amount of Pulls* and *Time of Delivery after Application of Vacuum Extractor.* ***Maternal Patient Problems:*** *Perineal Tear* and *Creation of Episiotomy.* ***Neonatal Patient Problems:*** *Category Head Trauma, Mortality* and *Apgar Score*. ***Successful Procedure:*** *First Vacuum Device Success.* ***Generic Information:*** *Parity, Maternal Age, Birth Weight, Gestational Age* and *Procedural Information (Indication for VE, Position of Fetal Head, Regional Analgesia, Position of Application Cup, Station of Delivery* and *Operator Status*). It is recommended to use the above-mentioned as primary end-points in any further clinical vacuum extractor validation study.

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APPENDIX

A. Search Terms

TABLE III
SEARCH STRINGS INSERTED IN THE DATABASES ON 30-03-2022

Database	**Search Strings**
SCOPUS	(TITLE-ABS-KEY ("Vacuum Extrac*" OR kiwi AND cup* OR omnicup OR ventouse* OR vacuum AND assisted* AND deliver*)) AND (TITLE-ABS-KEY (clinic* AND trial* OR clinic* AND evaluation* OR validat* OR comparison* OR efficacy OR observational AND study)) AND PUBYEAR $>$ 2000
MEDLINE	(("vacuum assisted deliveries"[Title/Abstract]) OR ("vacuum assisted delivery"[Title/Abstract]) OR (vacuum extract[Title/Abstract]) OR (Kiwi omnicup[Title/Abstract]) OR (Omnicup[Title/Abstract]) OR (ventouse[Title/Abstract]) OR (vacuum pump [Title/Abstract]) NOT (forceps[Title]) NOT (cesarean[Title]) NOT (wound therapy[Title])) AND (((clinic*[Title/Abstract]) OR (efficacy[Title/Abstract]) OR (trial[Title/Abstract]) OR ("observational study"[Title/Abstract]))) AND (2000:2022[pdat]) AND (english[Filter])

B. Clavien-Dindo Scores

TABLE IV
PATIENT PROBLEMS FOUND IN THE FDA WITH CORRESPONDING CLAVIEN-DINDO SCORES

Patient Problem	**Clavien-Dindo Score**	**Neonatal/Maternal Problem**
(Cephalo)hematoma	4	Neonatal
Hemorrhage	4	Neonatal
Skull Fracture	3	Neonatal
Scalp Abrasion	3	Neonatal
Brain Injury	4	Neonatal
Swelling	1	Neonatal
Head Injury	1	Neonatal
Tachycardia	2	Neonatal
Bruising	1	Neonatal
Death	5	Neonatal
Fetal Distress	4	Neonatal
Bone Fracture(s)	3	Neonatal
Bradycardia	2	Neonatal
Suffocation	4	Neonatal
Bacterial Infection	2	Neonatal
Pain	1	Neonatal
Seizures	4	Neonatal
Pallor	2	Neonatal
Low Oxygen Saturation	2	Neonatal
Exposure to Body Fluids	2	Neonatal
Shock, Traumatic	4	Neonatal
Vaginal Rupture	3	Maternal
Edema	1	Maternal
Occlusion	3	Maternal
Hypoxia	2	Maternal

C. Patient Problems Incidence in FDA

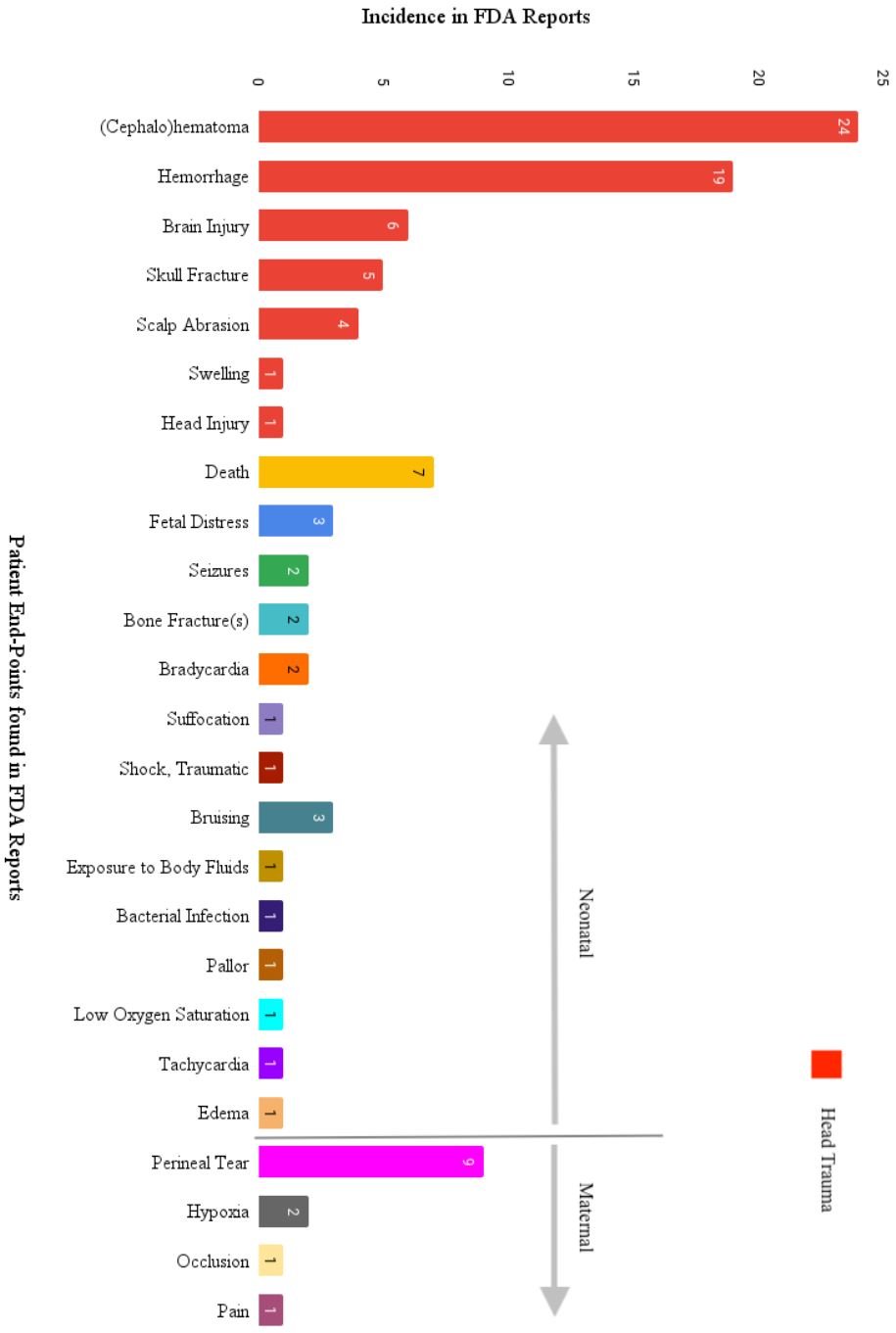

Fig. 13. The incidence of the patient problems found in the FDA reports

D. Clavien-Dindo & Incidence for Patient Problems in FDA

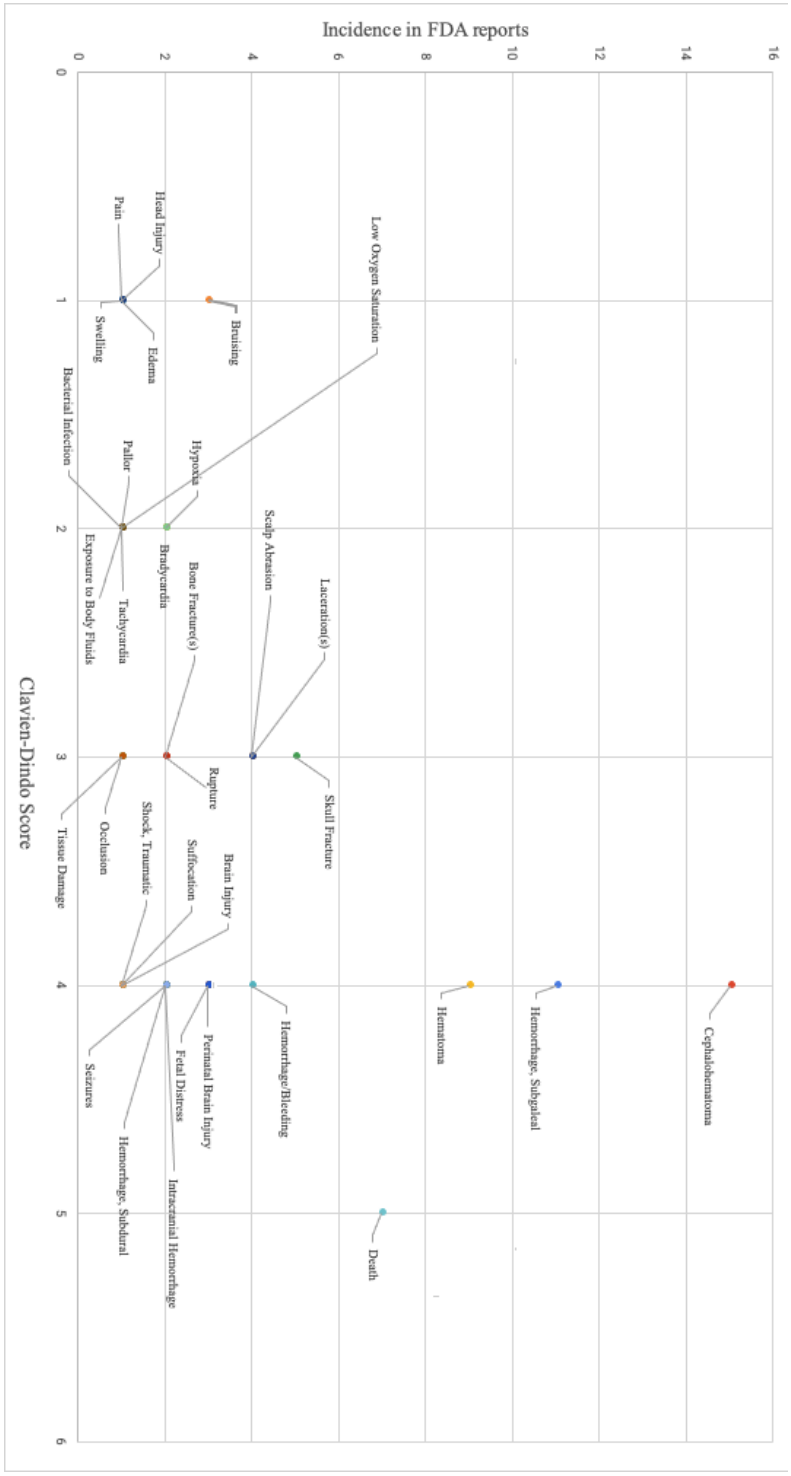

Fig. 14. The incidence versus the Clavien-Dindo score of each patient problem found in the FDA reports

E. Definitions I

TABLE V
DEFINITIONS OF END-POINTS FOUND IN THE SCIENTIFIC ARTICLES

Category	**Subcategory**	**End-Point**	**Definition**	% used as end-point in 32 scientific articles
Device Problems		Detachment of vacuum extractor	Detachment or pop-off of the VE cup with the head of the neonate	69%
		Amount of pulls	Amount of pulls a clinician performs with the VE before the neonate is delivered	47%
		Time of delivery after application ventouse	Time starting from the moment of application of the VE until the moment the neonate is delivered	38%
		Maximum traction force	Amount of force that a clinician exerts on the VE in a pulling movement	16%
Patient Problems	Maternal	Perineal tears	Injury to the tissue around the vagina	81%
		Creation of episiotomy	Creation of an incision in the perineum of the mother	66%
		Blood loss/haemorrhage	Any blood loss of the mother	50%
		Cervical tears	Injury to the tissue of the cervix	16%
		Mortality	Death of the mother	13%
		Infection	Any infection to the mother	13%
		Perineal pain at 24– 48 hours after delivery	Pain at the perineum of the mother at 24 – 28 hours after the delivery of the neonate	6%
		ICU admission	Admission of the mother to the Intensive Care Unit due to any complications regarding the delivery	6%
		Perineal pain 10 days after delivery	Pain at the perineum of the mother 10 days after the delivery of the neonate	3%
	Neonatal	Cephalohematoma	Blood that gathers between the scalp and the skull of a newborn [43]	72%
		Subgaleal hematoma	Blood that gathers between the scalp and the skull of a newborn [44]	44%
		Abrasion	Any scalp abrasion of the neonate	34%
		Scalp Lacerations	Any scalp lacerations of the neonate	28%
		Bruising	Any scalp bruising of the neonate	25%
		Caput succedaneum	Swelling of the scalp of a neonate [45]	19%
		Intracranial hemorrhage	Hemorrhage between the brain and the skull, or inside the brain tissue [46]	19%
		Fractures	Any scalp fractures of the neonate	9%
		Subcutaneous hematoma	Hemorrhage of the head of the neonate just under the skin	6%
		Apgar score at 5 min	Indiction of how healthy the kid is outside the womb of the mother [47]	72%
		Apgar score at 1 min	Indication of how well the infant withstood the labor and delivery procedure [47]	38%
		NICU admissions	Admission of the neonate to the Neonate Intensive Care Unit	41%
		Jaunice	Yellow discoloration of the skin and eyes of a neonate [48]	34%
		Phototherapy	The treatment of neonate jaundice	34%
		Shoulder dystocia	One or both of baby's shoulders gets stuck during delivery [49]	31%
		Mortality	Death of the neonate	28%
		Umbilical cord pH	The blood pressure in the umbilical cord	25%
		Intubation/Resuscitation	The need for intubation or resuscitation of the neonate	25%
		Facial nerve palsy	Loss of voluntary muscle movement in the face of a neonate [50]	16%
		Brachial plexus injuries	Any injury to the brachial plexus nerve group, resulting in a loss of movement [51]	9%
		Seizures	Epileptic shocks of the neonate	6%
		Retinal haemorrhage	Bleeding of any part of the neonate's eye	6%
Successful Procedure		First vacuum device success	Successful first attempt delivery with the VE	91%
		Delivery by caesarean section	Unsuccessful delivery with the VE and successful delivery with a caesarean section	53%
		Delivery by forceps	Unsuccessful delivery with the VE and successful delivery with a forceps device	53%
		Delivery by different vacuum device	Unsuccessful delivery with the VE and successful delivery another VE	47%
Clinical and Patient Experience		Doctors' ease of use	The score which the doctor assigns the overall procedure	28%
		Maternal satisfaction	The score which the mother assigns the overall procedure	6%
Generic Information	Maternal Info	Parity	The number of times a woman has given birth before	88%
		Maternal Age	The age of the mother	84%
		Disorders	Any medical disorders of the mother	19%
		BMI	The Body Mass Index of the mother	9%
		Weight	The weight of the mother	6%
		Height	The height of the mother	6%
		Race	The race of the mother	6%
		Married	A legal marriage of the mother	3%
	Neonatal Info	Birth weight	The weight of the neonate after the delivery	88%
		Gestational Age	The length of the pregnancy at the time of delivery	78%
		Head circumference	The measurement of the neonate's head at the largest point	9%
	Procedural Info	Indication for VE	The reason why a VE procedure was chosen	81%
		Station of Delivery	The measurement of the baby relative to the ischial spines [52]	59%
		Position of fetal head	The position of the neonate's head in the birth canal	50%
		Regional analgesia	Any use of anaesthetics on the mother	44%
		Position of application cup	The position where the cup is placed on the neonate's head by the clinician	31%
		Operator status	The status of the VE operator on a clinical scale	31%
		Duration of delivery	The total duration of delivery from the breakage of waters until the delivery of the neonate	22%
		Delivery in theatre	If the delivery happened in a clinical setting	6%

F. Definitions II

TABLE VI
DEFINITIONS OF END-POINTS FOUND IN THE FDA REPORTS

Category	**Subcategory**	**End-Point**	**Definition**
Device Problem		Suction Problem	Any problem related to the incorrect suction of the cup before or during the procedure
		Break of Device	Any disconnection of a part of the VE from the VE
		Incorrect Procedure	Any incorrect operation of the user of the VE
		Deflation Problem	Any problem related to the deflation of the VE after the procedure
		Entrapment of Device	Any entrapment of the VE inside the mother
		Pumping Problem	Any problem related to the pumping movement to create the vacuum
Patient Problem	Neonatal	(Cephalo)hematoma	Blood that gathers between the scalp and the skull of a newborn [43]
		Hemorrhage	Any bleeding of the neonate
		Brain Injury	Any injury on the brain of the neonate
		Skull Fracture	Any scalp fractures of the neonate
		Scalp Abrasion	Any scalp abrasion of the neonate
		Swelling	Any swelling of the neonates head
		Head Injury	Any injury on the head of the neonate
		Death	Death of the neonate
		Fetal Distress	A state of the neonate is not enough oxygenated
		Seizures	Epileptic shocks of the neonate
		Bone Fracture(s)	Any fractures of a bone of the neonate
		Bradycardia	A low heart rate of the neonate
		Suffocation	Any blockage of the breathing of the neonate
		Shock, Traumatic	Insufficient oxygen delivery [53]
		Bruising	Any bruising of the neonate's body
		Exposure to Body Fluids	Any contact of body fluids of the mother onto the neonate
		Bacterial Infection	Any bacterial infection of the neonate during or after the delivery
		Pallor	Paleness of the neonate's face
		Low Oxygen Saturation	Low oxygen value in the blood of the neonate
		Tachycardia	A high heart rate of the neonate ($>$100 beats a minute)
		Edema	Excess fluid trapped in the neonates tissues [54]
	Maternal	Perineal Tear	Injury to the tissue around the vagina
		Hypoxia	A condition in which there is insufficient oxygen at the tissue level to sustain appropriate homeostasis [55]
		Occlusion	The blockage of a maternal blood vessel
		Pain	Any maternal pain

Questionnaire for Participants | B

Questionnaire Participants

After success with Vela

1. On a scale of 1 - 4, how satisfactory did the Vela perform?

After success with Kiwi

2. On a scale of 1 - 4, how satisfactory did the Kiwi perform?

1 = extremely satisfactory
2= satisfactory
3 = unsatisfactory
4 = extremely unsatisfactory

After both vacuum extractions

3. On a scale of 1 - 3 (better/equal/worse), how was the **placement** of the Vela compared to the Kiwi?

4. On a scale of 1 - 3 (better/equal/worse), how was the **pumping** of the Vela compared to the Kiwi?

5. On a scale of 1 - 3 (better/equal/worse), how was the **pulling** with the Vela compared to the Kiwi?

6. What is your overall opinion of the Vela, and what are the differences compared to the Kiwi?

Informed Consent Form C

Proefpersoneninformatie voor deelname aan medisch-wetenschappelijk onderzoek

Comparison of the Vela Vacuum Extractor and the Kiwi Omnicup

Beste deelnemer,

Met deze informatiebrief willen we u vragen of u wilt meedoen aan medisch-wetenschappelijk onderzoek. Meedoen is vrijwillig. U krijgt deze brief omdat u een gynaecoloog (in opleiding) bent en u ervaring heeft met vacuüm extracties. Allereerst willen we weten of u geschikt bent als participant aan dit onderzoek. Als u de toestemming heeft zelf een vacuüm extractie uit te voeren en in het CWZ/LUMC werkt, bent u geschikt als participant.

U leest hier om wat voor onderzoek het gaat, wat het voor u betekent, en wat de voordelen en nadelen zijn. Wilt u de informatie doorlezen en beslissen of u wilt meedoen? Als u wilt meedoen, kunt u het formulier invullen dat u vindt in bijlage B.

1. Algemene informatie

U wordt uitgenodigd om deel te nemen aan een onderzoek genaamd “Comparison of the Vela Vacuum Extractor and the Kiwi Omnicup in a Randomized Mannequin Study”. Dit onderzoek wordt uitgevoerd door Iris Meijer van de TU Delft, prof. dr. T. van den Akker van het LUMC, dr. B. Nolens van het CWZ Nijmegen en prof. dr. J. Dankelman van de TU Delft.

2. Wat is het doel van het onderzoek?

Het doel van deze studie is het vergelijken van de Vela vacuüm-extractor en de Kiwi Omnicup, door vacuüm-extracties uit te voeren op de ‘Lucy and her Mum’ simulator.

3. Wat is de achtergrond het onderzoek?

Aangezien moeder- en neonatale sterfte een ernstig probleem blijft in landen met lage hulpbronnen en gedeeltelijk kunnen worden voorkomen met de toepassing van vacuümextractie, kunnen ziekenhuizen baat hebben bij de (her)invoering van vacuümextractie. Hoewel de afzonderlijke prijs van het device relatief laag is, zorgt het wegwerpkarakter voor een hoge onderhoudsprijs en een constante vraag naar nieuwe voorraden. Als gevolg van een gebrek aan financiële middelen, kunnen low-resource instellingen de vacuüm-extractoren niet veroorloven.
Om vacuüm-extractoren toegankelijker te maken in landen met weinig hulpbronnen, is Layco Medical een herbruikbare, goedkope en gemakkelijk te gebruiken vacuüm-extractor aan het ontwikkelen, de Vela. In deze studie is de doelstelling om de Vela te vergelijken met een veelgebruikte vacuüm-extractor, de Kiwi Omnicup.

4. Hoe verloopt het onderzoek?

Doet u mee met het onderzoek? Dan duurt dat in totaal ongeveer 20 minuten.
Er zult u gevraagd worden twee vacuüm-extracties te verrichten bij de mannequin ‘Lucy and her mum’. Dit zal één keer gebeuren met de Vela vacuüm-extractor, en één keer met de Kiwi Omnicup. De volgorde hiervan zal bepaald worden door randomisatie. Na elke vacuüm-extractie zult u gevraagd worden hoe het device presteerde. Na beide vacuüm-extracties zullen een aantal aanvullende vragen gesteld worden, waarvan één open vraag zal worden vastgelegd door middel van een audio-opname.

5. Wanneer stopt het onderzoek?

Als beide vacuüm-extracties voorbij zijn en de vragen beantwoord zijn stopt het onderzoek. Als u zelf wilt stoppen met het onderzoek mag dat op ieder moment. Meld dit dan meteen bij de onderzoeker. U hoeft er niet bij te vertellen waarom u stopt.

6. Wat doen we met uw gegevens?

De verkregen data zal anoniem verzameld worden. Ook zal er geen persoonlijke of tot op de persoon herleidbare data verzameld worden, behalve de audio-opname. Deze zal getranscribeerd worden, en de opname zal vernietigd worden. De geanonimiseerde data zal gebruikt worden voor een afstudeeronderzoek van de TU Delft en een eventuele publicatie in een wetenschappelijke journal.

7. Krijgt u een vergoeding als u meedoet aan het onderzoek?

U krijgt geen vergoeding als u meedoet aan dit onderzoek.

8. Heeft u vragen?

Vragen over het onderzoek kunt u stellen aan Iris Meijer, Barbara Nolens of Thomas van den Akker.

9. Hoe geeft u toestemming voor het onderzoek?

Wilt u meedoen? Dan vult u het toestemmingsformulier in dat u bij deze informatiebrief vindt.
Dank voor uw tijd.

Bijlage A: contactgegevens

Uitvoerende onderzoeker
Iris Meijer
Tel: +316 53505610
Mail: i.e.meijer@student.tudelft.nl

Bijlage B: toestemmingsformulier proefpersoon

Behorende bij *Comparison of the Vela Vacuum Extractor and the Kiwi Omnicup*.

- Ik heb de informatiebrief gelezen. Ook kon ik vragen stellen. Mijn vragen zijn goed genoeg beantwoord. Ik had genoeg tijd om te beslissen of ik meedoe.
- Ik weet dat meedoen vrijwillig is. Ook weet ik dat ik op ieder moment kan beslissen om toch niet mee te doen met het onderzoek. Of om ermee te stoppen. Ik hoef dan niet te zeggen waarom ik wil stoppen.
- Ik geef toestemming om mijn geanonimiseerde gegevens en audio-opname te verzamelen en te gebruiken. De onderzoekers doen dit alleen om de onderzoeksvraag van dit onderzoek te beantwoorden.
- Ik weet dat voor de controle van het onderzoek sommige mensen al mijn gegevens kunnen inzien. Die mensen staan in deze informatiebrief. Ik geef deze mensen toestemming om mijn gegevens in te zien voor deze controle.
- Ik wil meedoen aan dit onderzoek.

Mijn naam is (proefpersoon): .....

Handtekening: ..... Datum : _____ / _____ / _____

Ik verklaar dat ik deze proefpersoon volledig heb geïnformeerd over het genoemde onderzoek.

Naam onderzoeker (of diens vertegenwoordiger):

Handtekening:..... Datum : _____ / _____ / _____

Ethical Approval METC | D

afdeling METC LDD
postzone P5-P
Dr. M.A. van Santen

telefoon (071) 526 3241 fax (071) 526 6963
e-mail metc-ldd@lumc.nl
onze referentie **N22.099**/MS/ms
uw referentie

aan De weledelzeergeleerde heer
dr. T.H. van den Akker

afdeling Verloskunde

postzone K6-P, alhier

datum 12 oktober 2022
onderwerp **Niet WMO-MDR verklaring N22.099**

Geachte heer Van den Akker,

De medisch-ethische toetsingscommissie Leiden Den Haag Delft (METC LDD) heeft in de vergadering van haar dagelijks bestuur van 30-09-2022 het onderzoek besproken getiteld "Comparison between the VeLa Vacuum Extractor and the Kiwi Omnicup: a Randomized Non-Inferiority Mannequin Study", METC-nummer N22.099.

De METC LDD heeft de volgende documenten bij haar beoordeling betrokken:
- A1 Aanbiedingsbrief indiener d.d. 20-07-2022
- A1 Niet-WMO vragenlijst
- C1 Onderzoeksprotocol versie 4 d.d. 12-09-2022
- D2 IMDD versie 1 d.d. 20-07-2022
- E1 E2. Informatiebrief en toestemmingsformulier versie 2 22-09-2022
- F1 Vragenlijst Questionnaire versie 2 d.d. 14-09-2022
- K1 Goedkeuringsbrief wetenschapscommissie LUMC Obstetrie Gynaecologie d.d. 19-09-2022
- K6 Risk Analysis Vela
- K6 VELA Data Management Plan version 1 d.d. 06-07-2022

De METC LDD is van oordeel dat bovengenoemd onderzoek niet onder de Medical Device Regulation (MDR) valt. Dit onderzoek maakt gebruik van een of meerdere medische hulpmiddelen maar is geen klinisch onderzoek onder de MDR.

Ook valt het onderzoek niet binnen de reikwijdte van de Wet medisch-wetenschappelijk onderzoek met mensen (WMO), aangezien er geen sprake is van wetenschappelijk onderzoek zoals bedoeld in artikel 1, eerste lid onder b van de WMO.

Voor dit onderzoek is geen positief oordeel van een METC nodig.
Het protocol is niet inhoudelijk getoetst door de METC LDD.

De METC LDD verzoekt u iedere toekomstige wijziging van het onderzoek aan haar voor te leggen als door de wijziging het onderzoek mogelijk onder de reikwijdte van de MDR of WMO zou kunnen gaan vallen. U kunt hiervoor de website van de CCMO of METC LDD raadplegen. Bij twijfel kunt u contact opnemen met de METC LDD.

Ten slotte wijst de commissie u erop dat het uw verantwoordelijkheid is ervoor te zorgen dat uw onderzoek wordt uitgevoerd binnen de kaders van de geldende wet- en regelgeving, zoals de ‘Wet op de geneeskundige behandelingsovereenkomst’ (WGBO) en de ‘Algemene Verordening Gegevensbescherming’ (AVG)

Met vriendelijke groet,
namens de METC Leiden Den Haag Delft,

Dr. M.A. van Santen
secretaris

Aangezien voor deze brief geen wettelijke verplichting tot ondertekening geldt, wordt deze brief zonder handtekening verzonden.

Bijlage: 1. Approval for exemption from review

Cc: prof. dr. J.M.M. van Lith, Verloskunde, LUMC, Leiden
I.E. Meijer, TU Delft, Delft

Bijlage 1

Approval for exemption from review

To whom it may concern,

Referring to our letter dated 12-10-2022 on research protocol "Comparison between the VeLa Vacuum Extractor and the Kiwi Omnicup: a Randomized Non-Inferiority Mannequin Study", reference number N22.099, we are pleased to confirm that that neither the Medical Device Regulation (Regulation (EU) 2017/45 on Medical Devices) nor the Medical Research Involving Human Subjects Act (Dutch abbreviation: WMO) apply to the above mentioned study. Therefore, it is exempt from review by our Committee.

Yours sincerely,
on behalf of the Medical Research Ethics Committee Leiden Den Haag Delft

Dr. M.A. van Santen
Secretary

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