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| **Form - Summary of Use** |
| This Research Proposal must be submitted to the Research Committee convenor for consideration and approval by the committee prior to undertaking any research.  **Instructions on what should be considered when completing the relevant sections have been included in *italics*** |

**Proposed title of the project**

**A pilot trial of a novel medical device to alleviate pain during venepuncture**

**Principal Investigator**

**Dr Dave Listijono**

**Protocol Version number (e.g. v1.0):**

**v1.0**

**Date:**

**17/4/2023**

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# **List of all researchers who will be involved in the project**

All fields must be completed for each Researcher (add more lines if needed)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Role of the Researcher** | **Name**  **Email address** | **Virtus –affiliated? (Y/N)** | **If not Virtus-affiliated, what is the researcher’s institution?** | **Access to Virtus data needed?\*** |
| Principal investigator | Dave Listijono  Dave.Listijono@ivf.com.au | Y |  | N/A |
| Lead Virtus investigator  (if different from above) |  |  |  |  |
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**\*If yes, you MUST complete a data request form if the project is approved by the R&D Committee/ HREC – data will not be released unless this form is complete**

# **Objective(s) of the research**

*State the primary aim of your research? (one sentence)*

To assess the effectiveness of a novel medical device in alleviating pain during venepuncture.

*What is (are) the secondary aim(s)?*

To evaluate the impact of additional use of a medical device at the time of phlebotomy on venepuncture success rate.

# **Background**

The background should contain the following elements:

## **Problem Statement/ Relevance and Importance of the Research**

*Describe explicitly the theoretical or practical research problem that you want to address. What is already known about the problem? Include a discussion of existing literature. The literature review summarizes, compares, and critiques relevant academic sources on the topic.*

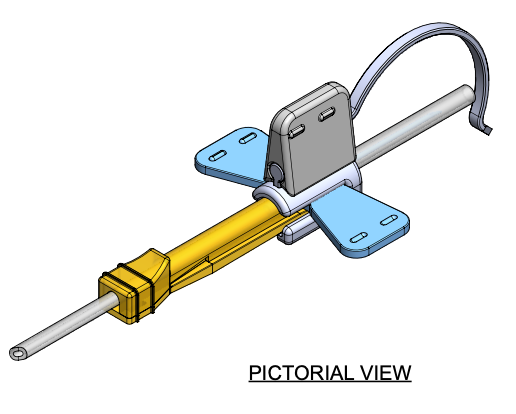
*What is missing from current knowledge? State the specific question(s) that you aim to answer. Make it clear what new insights you will contribute, who they are relevant to, and why the research is worth doing.*

Venepuncture to assess serum ovarian hormonal response has been the mainstay of monitoring of stimulated cycles in fertility treatment. The number of venepuncture events can vary from two in a simplified minimal stimulation cycle, to five or more in a standard controlled ovarian hyperstimulation (COH) cycle (Kwan et al, 2021), per patient. Anecdotally, the discomfort associated with repeated phlebotomy has been known to add to the anxiety and psychological stress in patients undergoing In-vitro fertilization (IVF) cycles. Therefore, approaches to reduce the pain of venepuncture present an attractive strategy to improve the overall IVF patient experience.

There are currently a limited number of tools available to chemically reduce the pain associated with venepuncture; the most widely used of which is the topical anaesthesic cream Eutectic Mixture of Local Anaesthetics (EMLA, 2.5% lidocaine and 2.5% prolocaine). However, in addition to the limited analgesic benefit of this topical agent compared to placebo (Shahid et al, 2019), the need to apply EMLA 30-60 minutes pre-procedure poses a myriad of practicality issues, which have hampered its uptake in busy clinical settings (Baxter et al, 2013). Importantly, EMLA has, albeit rarely, been associated with systemic toxicity in paediatric patients (Tran & Koo, 2014) and chemical eye injury in aesthetic procedures (Patel et al, 2020).

More recently, a number of devices have attempted to utilise the gate-control theory of pain (Melzack & Wall, 1965), which posits that large-diameter non-nociceptive nerve fibres, when activated, provides a pre-synaptic inhibitory effect on the smaller-diameter nociceptive (*pain*) fibres. Buzzy® (MMJ Labs, Atlanta, GA, USA) is an innovative device, using a combination of a cooling ice-pack and a vibrating motor, which is currently marketed as a device to alleviate pain during venepuncture in children (Baxter et al, 2009). Locally, another device (NeedleCalm®) uses a combination of cold sensation and a mechanical stimulation pad to reduce pain associated with needle procedures. However, there is to date no clinical trial to assess the efficacy of the latter. Notably, the use of prolonged cold exposure in Buzzy® was associated with aberrant haematological parameters, specifically higher haematocrit and lower platelet numbers, leukocyte and differentials (Lima-Oliveira et al, 2014). Therefore, in addition to the considerable cost of these sophisticated apparatus, there appeared to be potential clinical concerns with the use of the aforementioned devices. Furthermore, there is dearth of information on the potential impact of vibrational movements on the accuracy and success rate of the phlebotomist.

We have developed and patented an inexpensive, non-invasive device (“*D-Tip*”) for the purpose of reducing pain associated with venepuncture. The *D-Tip* employs a detachable ‘distractor tip’ proximal to the needle tip of a phlebotomy device, wherein the distractor tip is configured to contact the tissue surface before and during insertion of the phlebotomy needle; thereby providing a stimulant to the non-nociceptive nerve fibres and, in effect, inhibiting adjacent pain fibred. Compared to existing devices in the market, the D-Tip is relatively inexpensive, non-invasive and does not require to be applied to the tissue prior to procedure. Preliminary feedback from patients and phlebotomists have been overwhelmingly positive, with significant reduction in pain during venepuncture and notably user-friendly.



*(Patent Application No. AU 2021204566 A1)*

We hypothesized that the use of the D-Tip device will significantly reduce pain associated with venepuncture, without reducing the success rates of the venepuncture procedure. We aim to undertake a small-scale single-centre, patient-blinded prospective trial in women undergoing routine phlebotomy procedures during cycle monitoring. The advantage of this patient population is the opportunity to compare pain sensation in patients undergoing venepuncture procedures during a relatively stressful time-period.

# **Research design and methods**

*Explain your approach to the research and describe exactly what steps you will take to answer your questions; include specific details of the following:*

(**NB:** The checklist at the end of this document provides guidance around what are important elements to include in the study design).

## **Study Design**

*State the Explain how you will design the research. Qualitative or Quantitative? Original data collection or primary/secondary sources? Descriptive, correlative, or experimental? Retrospective or prospective?*

Single-centre, single-operator, patient-blinded randomised controlled trial.

## **Laboratory and/or clinical trial methodology**

*Describe the experimental procedures/laboratory methods. What are the interventions/exposure factors? How will groups be allocated? If the study is randomized controlled trial, please describe the randomization process (when, how, by whom), allocation concealment and blinding. Describe how a participant will progress through treatments, procedures, assessments, and visits, where applicable.*

Using the Randomisation Generator function on GraphPad Prism version 9.5.1, Patients will be randomly allocated to either undergoing venepuncture using conventional system (control) or the D-Tip system (intervention), with the procedure performed by a single phlebotomist. All procedures will be undertaken using the 21G butterfly needle. After gaining written consent, patients will be required to face away from the target arm, hence *blinding* them to the intervention status. Immediately following completion of the procedure, patients will fill out a Questionnaire, including a VAS scale.

## **Participant inclusion and exclusion criteria**

*Describe and justify the eligibility criteria. What methods will be used to identify approach, recruit, and consent participants or to obtain samples?*

Patients attending blood tests during cycle monitoring at the Westmead IVF Australia clinic will be offered to participate in the study. Participant Information sheet will be available in the waiting area for potential patients’ perusal.

To minimize variability in the mindset of participants, patients who are attending phlebotomy for non cycle-tracking purpose (e.g. pregnancy test, screening blood tests) will be excluded. Patients who had previously participated in the study will also be excluded.

## **Data Sources**

*Describe the data that will be collected for this study and how it will be collected.*

Patients will complete a questionnaire which include the following variables:

* Basic patient demographics
* History of mental health illness, including needle phobia
* Level of discomfort as indicated on the VAS scale

## 

## **Endpoints**

*There can only be one Primary endpoint and this should be in accordance with your primary objective. For example, if your primary question is to evaluate whether treatment A is associated with the probability of live birth after IVF, the primary endpoint should be live birth, i.e. "Live Birth defined as the delivery of a live neonate at or after 22 weeks of gestation”*

The primary endpoint of the study is the pain level experienced by participants, as assessed by the Visual Analogue Scale (VAS). The secondary endpoint is the failure (or repeated attempt) rate by the phlebotomist.

## **Statistical Considerations**

*What is the sample size that will be required for this study? Describe the power calculations undertaken to determine the study sample size. If no power calculation was performed, present relevant justification. Remember that the power calculation should be based on your primary objective.*

*Please describe in detail the statistical analysis plan. Include type of analyses (including sensitivity and subgroup analyses), statistical software that will be used, p-value where statistical significance will be declared, how you will address the problem of multiple statistical testing etc.*

Continuous variables, such as VAS pain score, will be analysed using the Student’s t-test or analysis of variance with parametric or non-parametric tests. Categorical variables, such as the need for multiple attempts, will be analysed using the Fisher’s exact test. Data analysis will be performed using the GraphPad Prism version 9.5.1.

Hypothesising a 20% reduction of the VAS score between the control and intervention groups, 17 patients in each arm would be required to have an 80% power to detect a significant difference using the Student’s t-test (two-sided, a=0.05). Standard deviations for both groups were assumed to be 1.

## **Feasibility and ethical considerations**

*Address any potential obstacles, limitations and ethical or practical issues. How will you plan for and deal with problems? For example, address the issue of adequate recruitment (or collection of samples) and what is your plan in case things are not progressing as planned.*

Considering the average weekly number of phlebotomy procedures in the clinic to be 100, with approximately 30% being recurring patients for cycle monitoring, and assuming a 50% recruitment rate, we predict 15 participants on a weekly basis. To fulfil the sample size of 34, with a conservative 50% drop-out rate, we anticipate the recruitment phase to be completed within 4 weeks.

Due to the non-invasive and practical characteristic of the D-Tip device, we do not foresee any ethical dilemma. Nonetheless, there is a possibility that the novel system might result in higher pain sensation for patients. This will be closely monitored by the phlebotomist and principal investigator, taking into account real-time patient feedback.

## **Data storage and disposal**

*How will you ensure participant confidentiality is maintained? For example, in most research studies, identifying information of included participants (e.g. Name, DOB etc) should not be released. Who will have access to data? What are the legislative requirements for the length of time data should be kept and how will this be disposed of when the storage period expires?*

*Refer to the* ***Virtus Research Data Management Policy*** *for guidance around the appropriate use of research data.*

Following consent, each eligible patient would be allocated a specific number according to a coding system. This number will be used in all data and information stored, for the purpose of maintaining anonymity throughout the study. The coding system will only be available to the DL in an encrypted file, saved onto a password-protected computer. Thus, patient confidentiality is maintained throughout the study period.

Following conclusion of the trial, the coding system file which contain identifying patient details (name, hospital number etc) will be permanently destroyed. No hard-copy will be used throughout the study.

## **Resources for the project**

*If you are applying for research funding, you will need to include a detailed budget that shows how much each part of the project will cost.*

*If you are NOT applying for research funding, and the resourcing for your project will be supported by the organisation, you will still need to include detailed list of the resources that will be allocated to the project.*

*For example:*

|  |  |  |  |
| --- | --- | --- | --- |
| ***RESOURCE*** | ***ALLOCATION*** | ***SOURCE***  *(name of funding body)* | ***COST (AU$)*** |
| *D-Tip device* | *50 units @ $20 each* | *Prudenfort Pty Ltd* | *1,000.00* |
|  | | ***Subtotal (external):*** | *1,000.00* |
|  | | ***Subtotal (internal):*** | *N/A* |
|  | | ***TOTAL:*** | *1,000.00* |

# **References**

Baxter A, Ewing PH, Young GB, & Ware A (2013). EMLA application exceeding two hours improved pediatric emergency department venepuncture success. Adv Emerg Nurs Jour; 35(1):67-75.

Kwan I, Bhattacharya S, & Woolner A (2021). Monitoring of stimulated cycles in assisted reproduction (IVF and ICSI). Cochrane Database Syst Rev; 2021(4): CD005289.

Lima-Oliveira G, Lippi G, Salvagno GL, et al (2014). A new device to relieve venipuncture pain can affect haematology test results. Blood Transfus; 12 Suppl 1: s6-10.

Melzack R & Wall PD (1965). Pain mechanisms: a new theory. *Science*;150:971–9.

Patel S, Shamdas M, & Cobb C (2020). Plasma fibroblast skin tightening treatment resulting in bilateral chemical eye injury secondary to EMLA cream: a case report. BMC Ophthalmology;20:342.

Shahid S, Florez ID, & Mbuagbaw L (2019). Efficacy and Safety of EMLA Cream for Pain Control Due to Venipuncture in Infants: A Meta-analysis. Pediatrics; 143(1): e20181173.

Tran AN & Koo JY (2014). Risk of systemic toxicity with topical lidocaine/prilocaine: a review. J Drugs Dermatol;13(9):1118-22.

## **Anticipated timeline of the research**

|  |  |
| --- | --- |
| **Intended start date** | 15 May 2023 |
| **Interim time-points in the schedule**  (e.g.: ethics submission, patient recruitment, data analysis) |  |
| R&D Committee submission | 17 Apr 2023 |
| Ethics Committee submission | 1 May 2023 |
| Commencement of recruitment | 15 May 2023 |
| Completion of recruitment | 12 Jun 2023 |
| Completion of data analysis | 26 Jun 2023 |
| **Intended conclusion date** | 10 Jun 2023 |

## **Research Proposal Checklist**

The purpose of the checklist is to ensure the project is scientifically valid. All questions should be answered.

|  |  |  |
| --- | --- | --- |
| **CRITERIA**: *Using the right column please indicate if each criterion has been addressed* | | **YES**  **NO**  **n/a** |
| **Project details**: Has all appropriate information been included? (Investigator details and project title, protocol version number and date) | |  |
| **Research question**: Is there a clearly and precisely defined, answerable question? Is there a clear aim or objective? | |  |
| **Background**: Does the background information provided give a good rationale for why the project is being done? Is the study useful to clinical practice? Is there a real problem/knowledge gap that needs filling? | |  |
| **Plan of Investigation**: | | |
| 1 | **Design**: Is the design appropriate to the aim? Will the study address the question being asked and is it likely to produce an answer? |  |
| 2 | **Bias and confounding**: Has the study been designed to minimise the risk of bias? Have the investigators adequately accounted for the influence of potential confounders? |  |
| 3 | **Randomisation and Blinding**: Where applicable, is enough detail provided on exactly how randomisation and blinding will be achieved, including who is responsible? |  |
| 4 | **Sampling issues**: Will the proposed study group be large enough to provide sufficient statistical precision or power, where appropriate? Is there a reasonable justification for the proposed sample size? Will the sample collected be reasonably representative of the population in question? |  |
| 5 | **Feasibility**: Is there sufficient evidence to indicate that it will be possible to obtain the numbers required for the study? Is the study feasible in terms of funds, time and other resources? |  |
| 6 | **Participants/samples**: Are the criteria for eligibility clear and justified? Have the methods used to identify approach, recruit and consent participants or to obtain samples been clearly and completely described? |  |
| 7 | **Intervention or exposure**: Is the intervention or exposure factor clearly described in adequate detail, where appropriate? If the intervention is a drug, are details of dose, delivery, preparation, handling and compliance provided? |  |
| 8 | **Procedure plan**: Has an appropriate plan of the study been detailed? Is the estimated duration of the project stated and appropriated? Is it clear how a participant will progress through treatments, procedures, assessments and visits, where applicable? Are laboratory methods described adequate, where applicable? |  |
| 9 | **Outcome measures**: Are these appropriate and achievable? Are definitions sufficiently detailed? Are there relevant data being collected on the proposed outcomes? |  |
| 11 | **Data collection**: Are the proposed data collection tools and data management systems appropriate for the project? |  |
| 12 | **Analysis**: Is there an adequate indication of what analysis will be done on outcome measures to answer the research question? Are the proposed analyses appropriate? Is analysis by intention-to-treat? |  |
| 13 | **Project Management**: Have adequate arrangements been specified for conduct and oversight? Is there a Data Monitoring and Safety Committee? Are interim analyses planned, with appropriate stopping rules? Is there an appropriate flow diagram of the study? If an RCT – is it registered? Are all questionnaires and tests validated tools? Are non-validated questionnaires attached? |  |
| 14 | **Expertise**: Does the research team include (or have access to) all the necessary expertise for the project? |  |
| 15 | **Ethical issues**: Have any potential ethical issues been addressed? Are risks to participants minimised? |  |

**\*\*END OF DOCUMENT\*\***