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REFERENCES

PARAMEDI

WHY DIABETES IN AREAS OF CONFLICT?

During times of conflict, people with diabetes face numerous challenges, including food insecurity, insufficient access to medications and testing supplies, as well as not enough people with knowledge in diabetes care. Having access to insulin represents a major challenge during times of conflict, especially for individuals with type 1 diabetes, for whom not having sufficient insulin results in a medical emergency. (1)

INTRODUCTION

WHAT IS TYPE 1 DIABETES?

- Type 1 diabetes is a chronic condition that results in the destruction of insulin-producing **pancreatic beta cells**.
- **Insulin** is a hormone that is vital in supporting homeostasis by **lowering** blood glucose levels when they are too high.
- Glucose-excited neurons in the hypothalamus are activated by increased blood glucose levels.
- This sensory information is transmitted to neural activity regulators that control blood glucose levels in conjunction with the pancreas.
- The pancreas then increases insulin secretion, causing glucose to move from the blood into cells for respiration or into the liver where it can be converted into glycogen for storage.
- **537 million** adults globally suffer from either type 1 or type 2 diabetes.
- **3 in 4** of these sufferers live in **low and middle-income countries**. (2)

WHAT HAPPENS WHEN TYPE 1 DIABETES IS LEFT UNTREATED?

- When an individual with Type 1 diabetes does not receive their dosage of insulin, high blood glucose levels – **hyperglycemia**, sets in. Hyperglycemia leads to **diabetic ketoacidosis (DKA)**: where body cells do not receive a sufficient volume of glucose to aerobically respire in order to function, therefore the liver begins to break down body fats and muscles, converting them into ketones which will build up in the bloodstream and turn blood **acidic**: Diabetic Ketoacidosis. When untreated, DKA can result in mortalities within 72 hours. (3)

CHALLENGES

AFFORDABILITY

- Globally over 90% of the insulin market is dominated by **3 multinational pharmaceutical companies** - Eli Lilly, Novo Nordisk and Sanofi. (4)
- Different models of Afrezza are available at average wholesale prices ranging from **$271** for 90 4-unit cartridges plus two inhalers, to approximately **$380** for 60 8-unit cartridges, 30 12-unit cartridges, and two inhalers.
- In 2006, the cost of **Pfizer's Exubera insulin inhaler** was **$5 per day** whereby **subcutaneous insulin** at the time cost only **$2-3 per day**. It generated only **$4 million** in sales in its final quarter, indicating the **lack of demand** due to its higher price and lower efficacy in comparison to injectable insulin.
- However, research by the company **R-bio** has also found a process to **increase the rate of insulin production**, therefore **decreasing prices**, through creating a 'biosimilar' version of insulin known as **'R-biolin'.** This is done by using a **different sequence of amino acids** to code for a gene to produce more proteins than usual, insulin included. **Increasing the yield** of the drug would therefore d**ecrease the price** and increase affordability, making the product more practical for potential future use. If research is furthered this could potentially act as a development to the **cost effectiveness** of our product.
- Additionally, our choice of using donated parachutes would contribute to the **circular economy** as recycling and reusing old products would save money as well as resources.

A HUMANITARIAN CRISIS: WHAT ARE THE MAIN CHALLENGES OF ACCESSING INSULIN WITHIN CONFLICT ZONES?

- **Travelling** to healthcare centres in conflict areas to collect insulin can be dangerous, and many patients do not have access to transport. (5)
- Many civilians need to be shown by a healthcare professional how to safely use insulin pens which isn't possible due to **language barriers** and the **lack of trained healthcare professionals** in conflict zones.
- Due to a **lack of electricity** and limited access to a reliable supply of medication, many hospitals themselves are unable to store and hence provide insulin.
- Insulin is typically stored in **refrigerators** in homes between 2-6 degrees Celsius. However, refrigerators are not accessible in refugee camps, and civilians in their homes face a lack of electricity.
- Managing diabetes also requires the maintenance of a healthy diet. This is unattainable due to **food insecurity** in a conflict area. Mealtimes are also often randomised which can cause blood sugar spikes. Furthermore, **exercise**-which can increase insulin sensitivity and reduce post-meal blood sugar spikes, is limited in conflict zones.
- **Insulin pens** requires **needles** and syringes. These are very costly, difficult to keep sterile and are difficult to dispose of safely.
- 90% of the insulin market is controlled by 3 large pharmaceutical companies who set **unaffordable prices.**

STORAGE

Typically, insulin is stored in refrigerators in people's homes at a temperature between 2 and 6 degrees Celsius. Due to the lack of electricity, and consequently fridges, in areas of conflict, storage of insulin would be a great challenge to civilians, especially those taking shelter in refugee camps or those living in a hot climate. (6)

- In recent studies supported by the MSF, a **Zeer-pot refrigerator** which consists of 2 clay pots between which the gap is filled with wet sand, has proven to be an effective **cooling device** for the storage of insulin.
- Accompanied by a clay lid, an unglazed clay Zeer-pot refrigerator has proven to **reduce temperatures by up to 12 degrees** Celsius (dependent on humidity), making average temperatures at or close to standard room temperature achievable even in hot climates.

CLINICAL TRIALS

- r-Bio have completed lab testing of their newly proposed **R-biolin**. Hence, we have planned a clinical trial that would allow their insulin to be approved by the FDA.
- The study would contain a **stratified sample** that is reflective of the percentage of diabetes by age category in the U.S population. Hence, we would use 9% of people ages 18-44; 36% of ages 45-64; and 55% of people over 65.
- Participants of the trial must be screened prior for any pre-existing chronic conditions. Participants must not have any other underlying medical conditions (apart from type 1 diabetes). The participants would be monitored regularly, including the **recording of their blood glucose levels**. (10)

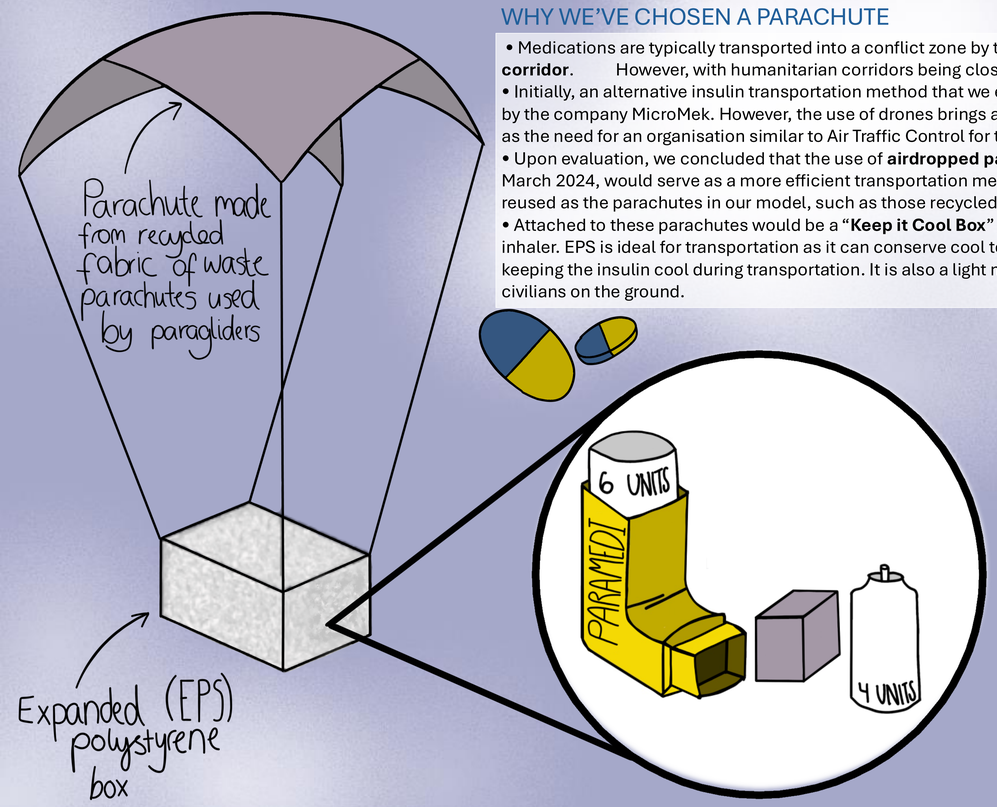
PHASE I:
- 60 **healthy volunteers**; 12 weeks; Test for **safety** and **dosage**

PHASE II:
- 300 **type 1 diabetes patients;** 26 weeks; Test for **efficacy** and **side effects**

PHASE III:
- 3000 **type 1 diabetes patients**
- The sample would be divided randomly into three equal sized groups
- A double-blind test would be carried out in which one group is given an existing model of the Afrezza inhaler which consists of a cartridge containing a new dry powder formulation of recombinant regular human insulin; one group is given Pfizer's 2006 model of the Exubera inhaler that uses fast-acting insulin powder; whilst the 3rd group is given our new Exubera model which uses a vial of R-biolin.
- 52 weeks
- Test for **efficacy** in comparison to the existing Afrezza inhaler and the original Exubera model

METHODOLOGY

Information was gathered through the use of **online resources** such as articles. Search engines such as PubMed, the NHS and pages which have been approved by prestigious and proficient institutions, were used to ensure that authors have **expertise** in their area of research. Information was cross referenced and referenced to increase the **accuracy** and **validity** of the data, and all resources, can be accessed via our QR code.



WHY WE'VE CHOSEN A PARACHUTE

• Medications are typically transported into a conflict zone by the use of **cold chain transportation** through a **humanitarian corridor**. However, with humanitarian corridors being closed down during conflict, this is not often possible. (7)
• Initially, an alternative insulin transportation method that we explored was the use of a low-cost, locally produced **drone** such as those produced by the company MicroMek. However, the use of drones brings about many challenges such as the need for approval of a drone corridor, as well as the need for an organisation similar to Air Traffic Control for the drones.
• Upon evaluation, we concluded that the use of **airdropped parachutes**, such as those used by the UK to transport food supplies to Gaza in March 2024, would serve as a more efficient transportation method. Emergency parachutes that are discarded by paragliding pilots would be reused as the parachutes in our model, such as those recycled and reused by the Swiss organisation, Humanitarian Pilots Initiative.
• Attached to these parachutes would be a "**Keep it Cool Box**" made of **expanded polystyrene** (EPS) which would contain the insulin vial and inhaler. EPS is ideal for transportation as it can conserve cool temperatures as low as 2-6 degrees Celsius for up to 48 hours, which is ideal for keeping the insulin cool during transportation. It is also a light material which is beneficial for transportation purposes and reduces danger to civilians on the ground.

OUR PRODUCT AND SOLUTION

- Our solution is to **deliver inhalers and vials** to areas of conflict. However, our vials will come in a **variety of sizes** each containing a different dosage in units of insulin, therefore all that needs to be done is select the appropriate number of units and insert the vial into the inhaler and administer it. (9)
- These inhalers and vials would be dropped in **expanded polystyrene (EPS) boxes**, since they are able to **conserve cool temperatures** as low as 2-6 degrees for up to **48 hours.**
- Our boxes would also contain a **comic instruction strip** for how to correctly use the inhalers (to ensure that the insulin is actually reaching the alveolar space so it can be absorbed into the blood stream), and how to create Zeer pots (so that they can keep the vials as close to a room temperature as possible).
- These EPS boxes would be attached to **recycled and reused donated parachutes** that would enable our boxes to reach the ground as safely as possible, while being sustainable and saving money and resources.
- Lastly once individuals have our inhalers, they would use the **Zeer pot refrigerator method** to keep the vials cool so that they may last for as long as possible in their climate.

WHY HAVE WE CHOSEN OUR INHALER?

- Currently the **only FDA approved** insulin inhaler is the **Afrezza** inhaler which consists of a dry powder inhaler and a new dry powder formulation of recombinant regular human insulin (Technosphere insulin), which is packaged in a pre-filled cartridge and delivered through a handheld pocket-sized device. However, costing **$99 per box**, this inhaler is **unaffordable.** (8)
- Our proposal is to **reintroduce an improved version** of Pfizer's 2006 model of the **Exubera** insulin inhaler. The product was **discontinued due to its high cost.** Hence, in our model we plan to **replace the fast-acting insulin powder** used in the original model with a **vial of R-biolin.** R-biolin vials (containing liquid insulin) would be inserted into an **aerosol inhaler** in which it can be vapourised and inhaled into the lungs through the mouth. This would make our product **more cost effective** due to R-biolin being **30% cheaper** than any other existing form of insulin.
- While inhalable insulin is **not as effective** as subcutaneous insulin, it is **more practical** for use in conflict zones as it is far easier to use (especially when combined with our cartoon instruction manual that is contained within our 'Keep It Cool Box'). Hence, healthcare professionals are not needed to show patients how to use the device. Additionally, sterile needles are not needed making our device far safer for patients and our device is **more affordable** making it more accessible to those in conflict zones.

MEDICAL ETHICS

- **Efficacy -** Repeated injections can cause adverse reactions at the injection site such as lipoatrophy, which can affect insulin absorption and increase the frequency of glycaemic excursions. We therefore decided to use an **insulin inhaler**, which has proved **non inferior** to subcutaneous injections following clinical trials for improving glycaemic control to ensure effective patient centred care is maintained. (11)
- **patient satisfaction and willingness to adhere -** For insulin therapy, insulin needs to be taken in the form of regular subcutaneous injections—a substantial limitation that often discourages patients and leads to poor **treatment compliance**. The most notable advantage of inhaled insulin lies in the fact it is accepted more extensively by patients due to the lack of invasive methods such as needles, resulting in greater persuasion to begin treatment.
- **safety** - concern has been raised about the long-term effects of inhaled insulin in the lung. So far, no serious adverse effects have been seen increasing its promise, further influencing us to make use of the inhaler
- **social environment -** With our focus stemming on global health and settings involving conflict where environments are likely to be hectic, dangerous, and fast paced, we ensured the means of mass delivery were easy and fast, through the use of parachutes, and the instructions were clear and accessible to all, through the use of a small **visual instruction manual** alongside the inhaler (assist with language barriers).