March 1, 2019

# Abstract

Wound dressings are an essential part of care of surgical wounds left open to heal by secondary intention as wounds that are not regularly dressed are prone to delayed healing and accumulation of slough. Several materials have been used to enhance the growth of healthy tissue in surgical wounds by chemically debriding wound slough. One such material is the Edinburgh University Solution of Lime which is commonly used in Pakistan. However the efficacy of EUSOL gauze in accelerating wound healing has not been proven in literature as compared to normal saline soaked gauze. Morever, it is an expensive solution. There is a need to objectively establish the true benefit of EUSOL soaked dressings in comparison to normal saline soaked dressing in order to justify the cost to the patient.

# Introduction

According to Wilkins et al., debridement, irrigation and cleaning for the basis of wound care. Debridement involves mechanical removal of dead tissue, irrigation involves application of fluid streams to the wound under pressure and cleaning involves application of fluid to the wound. [Wilkins\_2013] These activities aim to reduce the amount of non-viable biological material on the surface of the wound. Non-viable biological material (such as fibrinous debris of dead skin) inhibits myofibroblasts (that grossly appear as granulation tissue) from growing into the wound. Wound care activities therefore increase the chances of wound healing.

To that end, history has seen the application of various materials to wounds. These materials range from herbal applications like turmeric to chemicals such as betadine and povidone-iodine. Normal saline and EUSOL are two materials commonly used in Pakistan. Normal saline consists of 0.9% sodium chloride dissolved in water (or 152 mEq of NaCl). It is colorless and odorless. It's osmolarity is close to that of blood making it an "isotonic" fluid.

Smith et al. describe the Edinburgh University Solution of Lime (EUSOL) to be a highly diluted weak acid comprising 1.99 percent EUSOL against 98.01 percent water. The exact constituents of the Edinburgh University Solution of Lime are 0.54 percent hypochlorous acid, 1.28 percent calcium biborate and 0.17 percent calcium chloride. Therefore, it is essentially formed of the chemical reaction of boric and chlorate salts. In this chemical composition, EUSOL is volatile and decomposes into hypochlorous acid and sodium chloride. This process is accelerated in the presence of light therefore EUSOL is stored in photo-resistant containers. [Smith\_1915]

### Mode of Action

Edmiston et al. found normal saline to have the following advantages: it hydrates the wound bed. It also reduces the burden of biological material thereby expediting wound healing process. [Edmiston\_2016]

The antiseptic properties of EUSOL were known as far back as 1990s whereby experiments show its effectiveness against streptococcus pyogenes among other pathogens. EUSOL has even been investigated as an intravenous agent in the treatment of the bubonic plague. [connor1916eusol]

Recently, EUSOL has also come to be known as a chemical debridement agent. [Farrow\_1991] It loosens slough (fibrinous, necrotic cellular debris) from the base of the wound. In doing so, it prevents the retardation of wound granulation (in-growth of new fibroblasts) and epithelialization (regeneration of the outermost layer of the skin). This theoretically reduces the time to wound healing. It also decreases the chance of wound infection as decreased slough means reduced nidus of bacterial colonization.

# Rationale

Wounds healing by secondary intention are at risk of developing a layer of fibrinous exudate (commonly termed as "slough"). Slough has the potential to arrest the formation of healthy granulation tissue as well as to elevate the risk of wound super-infection. Meticulous wound dressing involves addressing the appearance of slough on wound in order to mitigate the risks of delayed wound healing and wound super-infection. The Edinburgh University Solution of Lime is commonly added to dressing routines as a method of chemical debridement of slough.

Several problems remain with the use of EUSOL. The foremost problem is that EUSOL is expensive with the cost of averaging to 3 rupees per milliliter. This price may not be problematic for small wounds that require once daily dressing. However the price can climb steeply if the wounds are of large size or require multiple dressings within 24 hours.

Another problem, as detailed above, is that the chemical composition of EUSOL degrades with time. Therefore EUSOL cannot be purchased or stored in bulk quantity. Not all patients have the capacity to visit a pharmacy repeatedly to obtained more EUSOL when expired and this is especially a problem for patients living in remote areas.

Perhaps the most concerning point on using EUSOL for wound care is that its efficacy has remained controversial for well more than a decade. One of the first objections to the use of EUSOL for wound dressings appears in the 1990s. [Burton\_1992,Patton\_1992] These objections are narrated in letters to the editors where doctors describe events where they have been approached by other healthcare providers either discouraging or actively refusing the use of EUSOL in patient care. The NICE guidelines (NICE, 2019) categorically prohibits the use of EUSOL on wounds that are healing by secondary intention.

However, it is difficult to synthesize an evidence based opinion regarding EUSOL from the literature. To the knowledge of the authors, there exists no study directly comparing EUSOL dressing with simple gauze soaked in normal saline. Rather, all available studies focus on comparison of EUSOL dressing with a variety of other dressing materials. Table 1 summarizes these studies (see Appendix 1).

It is immediately obvious that no unified conclusion can be drawn from these studies. There is no single, uniform measure of wound healing across studies to allow objective comparison of the relative performance of EUSOL. Furthermore, none of the dressings materials described in these studies are commonly used in Pakistan for dressing wounds healing by secondary intention.

In summary, the rationale of this study is the need for effective and inexpensive dressing to address the slough that frequently appears on surgical wounds healing by secondary intention.

### Study Hypotheses

Null: The healing rate of open surgical wounds dressed with EUSOL dressings is not greater than that of open surgical wounds dressed with Normal Saline dressings.

Alternate: The healing rate of open surgical wounds dressed with EUSOL dressings is greater than that of open surgical wounds dressed with Normal Saline dressings

### Primary Objective

To determine whether the healing rate of open surgical wounds healing by secondary intention is significantly greater when cleansed with EUSOL dressing as compared to normal saline dressing.

# Methods and Materials

## Operational Definitions

* **Wound Healing Rate**:: The value θ of the delayed exponential curve plotted on a graph of advance of wound margin towards the wound center against time since surgery for a set of seven or more wound measurements such that:
  + The two longest, mutually perpendicular diameters of the wound, *a* and *b* measured in mm, are used to calculate the area of the wound, *S* in mm2, using the formula $$ \frac{\pi}{4}a\_i\cdot b\_i $$ and the perimeter, *p* in mm, of the wound using the formula \(\pi[\frac{3}{4}(a\_i+b\_i)-\frac{1}{2}\sqrt{a\_0\cdot b\_0}]\)
  + The advance of wound margin, in mm, towards the center of the wound is calculated using the formula \(2\frac{S\_0}{p\_0T}[mm/day]\)
  + The seven measurements are taken at an interval of one week. [Cukjati\_2001]
* The predicted time, in days, for a given wound to reduce to 5% of its initial area or the predicted time for a given wound to reduce to less than 100 mm2 which ever is smaller. This definition has been adapted from Cukjati et al. [Cukjati\_2001]
* **Diabetic Patient**:: Patients with reduced ability to auto-regulate serum glucose levels as defined by guidelines of the National Institute of Health and Care Excellence, United Kingdom [ICGT\_2015]:
  + Documented fasting blood glucose level > 125 mg/dL
  + Documented random blood glucose level > 200 mg/dL
  + Documented HbA1c > 6.5 mg/dL
  + Taking oral hypoglycemic agents
  + Taking subcutaneous insulin injection
* **Smoking Status** and **Cigarette Usage**:: Cigarette usage as defined by the Centers of Disease Control and Prevention, USA [CDC\_Smoking]
  + **Every day smoker**
    - An adult who has smoked at least 100 cigarettes in his or her lifetime, and who now smokes every day. Previously called a “regular smoker”.
  + **Former smoker**
    - An adult who has smoked at least 100 cigarettes in his or her lifetime but who had quit smoking at the time of interview.
  + **Never smoker**
    - An adult who has never smoked, or who has smoked less than 100 cigarettes in his or her lifetime.
* **Normal Saline Dressing**:: The practice of applying povidone-iodine to wound edges followed by washing wounds with at least 500 cc of normal saline before applying gauze in a clean or sterile fashion
* **EUSOL Dressing**:: The practice of applying povidone-iodine to wound edges followed by washing wounds with at least 500 cc of normal saline before applying gauze soaked in EUSOL in a clean or sterile fashion
* **Open Surgical Wound**:: Surgical wound where skin has not been approximated by staples or sutures
* **Wound Care Practitioner**:: Wound Nurses, surgeons and/or surgical residents with at least one year of experience in dressing surgical wounds healing by secondary intention

## Study Design

This will be a single center, double-blinded, non-placebo-controlled, parallel-group study with balanced randomisation (1:1). The study will be conducted in Karachi, Pakistan whereby patients will be followed during both in-hospital stay as well as outpatients for a total of six weeks after surgery.

The unblinded data collected from each group will be reviewed by an independent investigator for patient safety. This independent investigator will assess each group for frequency of wound infections and of wounds that are non-healing. The study will be halted if 10% or more patients in either group suffer from wound infections or if 10 % or more patients in either group suffer from non-healing wounds.

## Study Setting

This study setting will be the Aga Khan University Hospital for inpatients as well as patients receiving home healthcare in the city of Karachi.

## Study Procedures

This study will involve the blinded use of normal saline and EUSOL in their assessment of wound healing capabilities. To that end, these solutions will be prepared, packaged and marked for use by the Aga Khan University Pharmacy Department.

Patients who have undergone any abdominal or limb surgery will be recruited (see [4.8](#anchor-22)) and assessed for eligibility (see sections [4.5](#anchor-23) & [4.6](#anchor-24)) . Eligible patients will be offered enrolllment in the trial using informed consent (see [7](#anchor-25)). The number of patients who are excluded from the study or who refuse to participate will be noted. Those who consent will be randomized to either the normal saline group or the EUSOL group as described in [8](#anchor-26).

Once randomized, the following details will be recorded for all patients using the "New Patient Registration" (see [9](#anchor-27))

* the patient's age and gender
* the surgery that the patient underwent and the date of that surgery
* whether the patient is a diabetic, smoker or has peripheral vascular disease
* the longest dimension of the wound and the second-longest dimension that is perpendicular to the first

Following initial registration, patients will recieve the allocated treatment as described in [8](#anchor-26). followed once a week for a total of 7 weeks. At each follow-up, the following details will be recorded using the "Follow-Up Wound Assessment" Form (see [9](#anchor-27))

* the longest dimension of the wound and the second-longest dimension that is perpendicular to the first
* whether the consultant surgeon of that patient has decided to close the wound surgically and the date of that decision
* whether the consultant surgeon of that patient has decided to retake the patient to OR for a re-look debridement and the date of that decision.

All wound assessments will be done by a wound nurse with at least one year of experience or by a consultant surgeon. At the end of the wound assessment period the collected data will be analyzed as per the analysis plan outlined below (see [4.13](#anchor-28)). The number of patients lost to follow-up and the number of patients who did not recieve the allocated treatment during the course of the study will be noted. These patients will be analyzed on an intention-to-treat basis. The entire study procedure is summarized in the consort diagram (see [6](#anchor-29)).

#+BEGINCOMMENT

### Intra- and Interobserver Variability Control

* Training on how to deal with parallax error
* Marking extent of measurement with parmanent marker at every time of measurement

### IRB form and application

### Follow Up Strategy

* Discuss the dangers of data collection using home health nursing care
* Discuss the possiblity of clinic follow-up for 6 weeks
  + Possibly using grant fund

#+ENDCOMMENT

## Inclusion Criteria

Tis study will include adult, post-operative patients with surgical wounds of the abdomen and limbs that have been left to heal by secondary intention.

## Exclusion Criteria

Patients with the following types of wounds will be excluded from this study:

* Wounds resulting from and/or complicated by viscero-cutaneous fistula: These wounds involve an abnormal connection between the epithelium of the skin and the epithelium of a hollow viscus that normally produces a bodily fluid. Wound care of viscero-cutaneous fistulas involves maneuvers to abate the physical and chemical effects of the bodily fluid to the skin. Such maneuvers have little or no connection with EUSOL. Therefore, wounds related to viscero-cutaneous fistulas are beyond the scope of this study.
* Wounds resulting from pre-existing dermatological pathology, for example (but not limited to) psoriasis: Wounds resulting from pre-existing dermatological pathology have a different natural history of healing as compared to wounds on otherwise normal skin. Management of such wounds typically involves medical regimens tailored to curtail the pathology causing the wound and wound healing is directly correlated to controlling that pathology. Therefore, these wounds are beyond the scope of this study.
* Wounds in patients on corticosteroid therapy
* Wounds in patients undergoing re-look debridement of the wound being studied

## Outcome Measure

The main outcome measure of this study will be the difference in mean healing rate between the normal saline and EUSOL groups. Healing rate will be calculated as defined by Cukjati et al. (see [4.1](#anchor-14)). The reader is referred to the full text for complete details.

## Sampling Technique

This study will recruit patients using consecutive sampling. Patients will be identified for recruitment on a daily basis using the Main Operating Room and Daycare Surgery Operating Room case list Recruitment will be attempted 24 - 48 hours after surgery.

## Randomization Technique

The patients will be randomly assigned to one of following two parallel groups in a 1:1 ratio:

* Normal Saline Dressings
* EUSOL Dressings

Randomization will be stratified by diabetic status, smoking status and presence of peripheral arterial disease. Following stratification, randomization will be done using block randomization technique using blocks of four, six and eight patients.

Randomization will be done by the Aga Khan University Clinical Trials Unit as described in [8](#anchor-26). This randomization table was generated using the online tool *Sealed Envelope* [simple\_rand\_serv].

## Blinding Technique

Preparation of the aliquots of normal saline and EUSOL will be conducted by the Aga Khan Hospital Pharmacy Department. EUSOL is a photosensitive compound (see [2](#anchor-2)) and must therefore be stored in tinted reagant bottles to prevent decomposition. To prevent identification of EUSOL from normal saline, aliquots of normal saline will also be stored in tinted reagent bottles.

Following preparation, the Aga Khan University Clinical Trials Unit will label the bottles. The labels will state the contents of the bottle and a randomization code from the table described in [8](#anchor-26).

Following labeling, aliquots will be allocated to patients who have been randomized to the same treatment arm as their contents. The Clinical Trials Unit will note the patient to whom each aliquot has been allocated on the randomization table next to the respective randomization code.

## Sample Size

The sample size for this study had been calculated on the basis of the work of Bajaj et al. [Bajaj\_2009] who compared the rate of wound healing in patients treated with sugar coated bandages with that of patients treated with EUSOL dressing. To the authors' best knowledge, there is no other study that more closely resembles the objectives of this study. Therefore, the authors saw fit to base sample size calculation upon this study.

Based on this study, the anticipated proportion of patients with wound healing in the standard dressing group (case group) is 77% and the anticipated proportion of patients with wound healing in the EUSOL dressing group (control group). Thus the relative risk of wound healing from normal saline dressing versus EUSOL dressing is expected to be 1.2.

The sample size was calculated using OpenEpi Software version 3.01. The sample size was calculated using the above anticipated proportions as well as significance of 5%, power of 80% and an inflation of 10% to account for non-response. The minimum sample size required was calculated to be 532 patients in total: 266 patients in Group 1 (standard dressing) and 266 patients in Group 2 (EUSOL dressing).

## Study Duration

The number of case records bearing the following ICD-9-CM codes in the last year were queried from the hospital database via The Aga Khan University Health Information Systems (HIS):

* Exploratory Laparotomy: 54.11 = 231
* Re-open Laparotomy: 54.12​ = 23
* Reversal of Colostomy: 46.52 = 35
* Carbuncle: 68.00 - 68.09 = 50
* Incision and Drainage of Abscess: 86.04 = 176
* Above Knee Amputation: 84.17 = 29
* Below Knee Amputation: 84.15 = 62

This query resulted in a total of 606 cases which exceeds the required sample size. Accounting for the 7 week follow-up required for each patient, this study is expected to take a maximum of 18 months to complete.

## Data Analysis

By measuring wounds with the method as defined by Cukjati et al. (see Operational Definitions), each wound will have a set of 7 measurements. These measurements will then be plotted on a graph of wound area against time. This graph follows a delayed exponential curve having coefficient θ. The coefficient θ will be calculated for all patients by fitting their individual wound measurements to the delayed exponential curve. Wounds having a faster healing rate will have a higher value of θ.

Student's t-test will be used to detect any significant difference in θ of patients in normal saline group and those in the EUSOL group.

# Appendix 1 Tables

Table 1: Summary of literature comparing EUSOL with various other wound dressing materials.

# Appendix 2 Consort Diagram

start :Assessed for eligibility (n= ); split :Excluded (n= )\n- Not meeting inclusion criteria (n= )\n- Declined to participate (n= )\n- Other Reasons (n= ); stop split again :Randomized (n= ); split :Allocated to Normal Saline Group (n= )\n- Received Allocated Treatment (n= )\n - Did not receive allocated treatment (n= ); :Lost to follow-up (give reasons) (n= )\n Discontinued Normal Saline treatment (n= ); :Analyzed (n= )\n- Excluded from analysis (n=); stop split again :Allocated to EUSOL Group (n= )\n- Received Allocated Treatment (n= )\n - Did not receive allocated treatment (n= ); :Lost to follow-up (give reasons) (n= )\n Discontinued Normal Saline treatment (n= ); :Analyzed (n= )\n- Excluded from analysis (n=); stop

# Appendix 3 Informed Consent

## 3a English Version

Study Title: Comparison of wound healing rate between EUSOL and Normal Saline Dressings

Principal Investigator: Dr. Rehman Alvi

Name of Organization: Aga Khan University Hospital

This informed consent has two parts

* Information Sheet containing details of the investigation that will be conducted during this study
* Certificate of Consent on which you may give your signature if you agree to participate

Part I: Information Sheet

I, Dr. Naveed Aman Pasha, work for Aga Khan University Hospital. We are doing a study on wounds that have been left open after surgery. We want to see if wounds heal faster if dressing is done with gauze soaked with normal saline as compared to gauze soaked with Edinburgh University Solution of Lime.

**Purpose of the Study**

Sometimes people undergo surgeries whereby surgeons do not close the wound with sutures but rather leave it open to heal by itself. This is usually because the surgery was done on an area that was dirty and/or infected so it is at higher risk of getting infected if closed with sutures. Such wounds are normally washed daily with normal saline after which they are dressed with gauze soaked in normal saline or EUSOL. EUSOL is thought to uproot the dead skin which develops during healing process to avoid stopping new, healthy skin from growing into the wound. However, EUSOL is an expensive solution. Moreover, the efficacy of EUSOL has been questioned world over. This research will compare the healing rate of wounds dressed with gauze soaked in EUSOL with that of those dressed with gauze soaked in normal saline.

**Participant Selection**

We are inviting all patients with open surgical wounds after their surgery to participate in this study.

**Voluntary Participation**

Your participation in this study is voluntary. Your choice to participate in this study does not affect the service you receive at the Aga Khan University Hospital. If you decide not to participate in this study you will continue to receive treatment routinely offered for dressing of open surgical wounds regarding which you will be informed later.

**Type of Research Investigation**

This research will involve a nurse or doctor measuring your wound during dressing change once a week for a total of six weeks. Measuring your wound will involve holding a ruler or measuring tape up to your wound and reading the value. It is a painless procedure.

**Description of Process and Duration of Study**

In this research, you will be assigned to one of two groups whereby your wound will be dressed with gauze soaked in normal saline or gauze soaked with EUSOL. Neither you nor your nurse/doctor will know which of the two your wound is being dressed with. This is necessary in order to keep the research process objective. Wound dressing will be done daily for a total of six weeks whereby your wound be measured every week as detailed above. After six weeks have elapsed and all measurements are complete your care will be resumed by your surgeon who will instruct you on how to dress your wound(s).

**Risks**

Any risk can appear during the study. Your progress will be monitored by our team of healthcare providers who will address any concerns if and when they arise.

**Benefits**

If you participate in this study, your daily dressings will be done free of charge. Your participation will also help us find out if doctors should actually be prescribing EUSOL which is an expensive solution. The results of this study can then be communicated to other medical experts so that society can benefit at large.

**Reimbursements**

Your participation is free and you will not be given any money or gifts to take part in this research.

**Confidentiality**

The persons involve in conducting this research will not share the identity of or disclose any information regarding patients who have agreed to participate in this study. The data collected during this research will be kept confidential. A stringent procedure is in place to ensure that data collected during this research is used only by persons conducting this study.

We are offering you participation in this study because you have undergone a surgery after which your wound(s) has been left open to heal. If you agree to participate in this study, you will be randomly assigned to one of two groups: dressings with EUSOL or dressings with normal saline.

Once you have been assigned, a doctor or nurse will dress your wound(s) with gauze soaked in either of EUSOL or normal saline everyday. Once a week, the nurse/doctor will measure your wound with a measuring tape and take a picture. This will continue for a total of six weeks.

## 3b Urdu Version

# Appendix 4 Randomization Table

# Appendix 5 Study Proforma

## 4a New Patient Registration

Use this proforma to register new patients into the study who have recently undergone surgery within the past 24 - 48 hours and fulfill the inclusion and exclusion criteria.

* Patient Details
  + MR Number: *\_*-*-*
  + Name: *\_\_*
  + Age: *\_*
  + Gender:
    - [ ] Male
    - [ ] Female
* Comorbidities:
  + [ ] Diabetic
  + [ ] Smoker
  + [ ] Peripheral Arterial Disease
* Details of the Surgery:
  + Surgery Performed:
  + Date of Surgery:
* Wound Measurement:
  + Longest Dimension (cm):
  + Perpendicular Dimension (cm):
  + Date of Measurement:

## 4b: Follow-Up Wound Assessment

Use this proforma to follow-up patients already enrolled in this study and record the dimensions and condition of the woun.

* Patient Details
  + MR Number: *\_*-*-*
  + Name: *\_\_*
* Wound Measurement:
  + Longest Dimension (cm):
  + Perpendicular Dimension (cm):
  + Date of Measurement:
* Wound Condition
  + [ ] Decision to close wound primarily
  + [ ] Decision to return to OR for re-look debridement
  + Date of Decision:

# Appendix 6 Reporting of Analysis

# References

[Wilkins\_2013] Robert Wilkins \& Martin Unverdorben, Wound Cleaning and Wound Healing, <i>{Advances in Skin \& Wound Care}</i>, <b>26(4)</b>, 160-163 (2013). <a href="https://doi.org/10.1097/01.asw.0000428861.26671.41">link</a>. <a href="http://dx.doi.org/10.1097/01.asw.0000428861.26671.41">doi</a>. [Smith\_1915] Smith, Drennan, Rettie \& Campbell, Experimental Observations ON THE ANTISEPTIC ACTION OF HYPOCHLOROUS ACID AND ITS APPLICATION TO WOUND TREATMENT, <i>{BMJ}</i>, <b>2(2847)</b>, 129--136 (1915). <a href="https://doi.org/10.1136Smith\_1915.pdfbmj.2.2847.129">link</a>. <a href="http://dx.doi.org/10.1136/bmj.2.2847.129">doi</a>. [Edmiston\_2016] Charles Edmiston \& David Leaper, Intra-Operative Surgical Irrigation of the Surgical Incision: What Does the Future Hold-Saline, Antibiotic Agents, Or Antiseptic Agents?, <i>{Surgical Infections}</i>, <b>17(6)</b>, 656-664 (2016). <a href="https://doi.org/10.1089/sur.2016.158">link</a>. <a href="http://dx.doi.org/10.1089/sur.2016.158">doi</a>. [connor1916eusol] Connor, Eusol and Plague: A Suggestion, <i>{The Indian Medical Gazette}</i>, <b>51(2)</b>, 73 (1916). <a href="">link</a>. <a href="http://dx.doi.org/">doi</a>. [Farrow\_1991] Farrow \& Toth, The place of Eusol in wound management, <i>{Nursing Standard}</i>, <b>5(22)</b>, 25--26 (1991). <a href="https://doi.org/10.7748Farrow\_1991.pdfns.5.22.25.s39">link</a>. <a href="http://dx.doi.org/10.7748/ns.5.22.25.s39">doi</a>. [Burton\_1992] Burton, For and against Eusol., <i>{BMJ}</i>, <b>304(6839)</b>, 1442--1443 (1992). <a href="https://doi.org/10.1136Burton\_1992.pdfbmj.304.6839.1442-b">link</a>. <a href="http://dx.doi.org/10.1136/bmj.304.6839.1442-b">doi</a>. [Patton\_1992] Patton, Eusol: the continuing controversy., <i>{BMJ}</i>, <b>304(6842)</b>, 1636--1636 (1992). <a href="https://doi.org/10.1136Patton\_1992.pdfbmj.304.6842.1636-a">link</a>. <a href="http://dx.doi.org/10.1136/bmj.304.6842.1636-a">doi</a>. [Cukjati\_2001] Cukjati, Reberšek \& Miklavčič, A reliable method of determining wound healing rate, <i>{Medical & Biological Engineering & Computing}</i>, <b>39(2)</b>, 263--271 (2001). <a href="https://doi.org/10.1007Cukjati\_2001.pdfbf02344811">link</a>. <a href="http://dx.doi.org/10.1007/bf02344811">doi</a>. [ICGT\_2015] Team, Type 2 Diabetes in Adults: Management, <i></i>, <b>(28)</b>, (2015). <a href="">link</a>. <a href="http://dx.doi.org/">doi</a>. [CDC\_Smoking] @misc{CDC\_Smoking, author = {Control, Centers for Disease and Prevention, }, title = {Adult Tobacco Use Information - Glossary}, year = {2017}, note = {Reviewed: 2017-08-29}, howpublished = {https://www.cdc.gov/nchs/nhis/tobacco/tobacco\_glossary.htm} } [simple\_rand\_serv] @Manual{simple\_rand\_serv, title = {Simple randomisation service}, organization = {Sealed Envelope Ltd.}, howpublished = {\textit{Available at \url{https://www.sealedenvelope.com/simple-randomiser/v1/}}}, OPTaddress = {}, OPTedition = {}, OPTmonth = {}, year = {2019}, OPTnote = {}, OPTannote = {} } [Bajaj\_2009] Bajaj, Karn, Shrestha, Kumar \& Singh, A randomised controlled trial comparing eusol and sugar as dressing agents in the treatment of traumatic wounds, <i>{Tropical Doctor}</i>, <b>39(1)</b>, 1--3 (2009). <a href="https://doi.org/10.1258Bajaj\_2009.pdftd.2008.080322">link</a>. <a href="http://dx.doi.org/10.1258/td.2008.080322">doi</a>. [Smith\_2013] Smith, Dryburgh, Donaldson \& Mitchell, Debridement for surgical wounds, <i>{Cochrane Database of Systematic Reviews}</i>, <b>()</b>, (2013). <a href="https://doi.org/10.1002Smith\_2013.pdf14651858.cd006214.pub4">link</a>. <a href="http://dx.doi.org/10.1002/14651858.cd006214.pub4">doi</a>. [Gethin\_2015] Gethin, Cowman \& Kolbach, Debridement for venous leg ulcers, <i>{Cochrane Database of Systematic Reviews}</i>, <b>()</b>, (2015). <a href="https://doi.org/10.1002Gethin\_2015.pdf14651858.cd008599.pub2">link</a>. <a href="http://dx.doi.org/10.1002/14651858.cd008599.pub2">doi</a>. [Reinar\_2019] Reinar, Forsetlund, Lehman \& Brurberg, Interventions for ulceration and other skin changes caused by nerve damage in leprosy, <i>{Cochrane Database of Systematic Reviews}</i>, <b>()</b>, (2019). <a href="https://doi.org/10.1002Reinar\_2019.pdf14651858.cd012235.pub2">link</a>. <a href="http://dx.doi.org/10.1002/14651858.cd012235.pub2">doi</a>. [Jull\_2015] Jull, Cullum, Dumville, Westby, Deshpande \& Walker, Honey as a topical treatment for wounds, <i>{Cochrane Database of Systematic Reviews}</i>, <b>()</b>, (2015). <a href="https://doi.org/10.1002Jull\_2015.pdf14651858.cd005083.pub4">link</a>. <a href="http://dx.doi.org/10.1002/14651858.cd005083.pub4">doi</a>.