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**Protocol for open randomised controlled trial investigating Fibrin Glue in Skin grafts for Skin cancer (FiGSS)**

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Protocol for open randomised controlled trial investigating Fibrin Glue in Skin grafts for Skin cancer (FiGSS)

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Abstract

Introduction

Skin cancer is a common disease in the tropics, and curative resection requires removal of large portions of skin which can only be replaced with skin grafts. Fibrin glue, initially established as a haemostatic agent, has been studied extensively as an adhesive for skin grafts in burns. This study aims to investigate the use of fibrin as an adhesive for split skin grafts in skin cancers.

Methods and Analysis

The study design is a prospective randomised controlled trial with the aim on investigating the impact on two different methods of split skin graft fixation. The intervention of fibrin glue will be compared to the control of staples or sutures. The trial will be conducted at two sites, a public and private hospital in Townsville, Australia over a 24 month period with 334 participants to be recruited. Consecutive patients presenting for skin excisions and grafting will be eligible to participate. Randomisation will be on the level of the patient. The primary outcome is graft take based on wound healing at one month. Secondary outcomes will be pain on dressing changes and operative time.

Ethics and Dissemination

The study has been approved by The Townsville University Hospital Human Research Ethics Committee (HREC). Findings will be disseminated in conference presentations and journals and through online electronic media.

Registration Details

Registered on Australian New Zealand Clinical Trials Registry ACTRN12618000484246

Discussion

This RCT is based in regional North Queensland which has the highest rate of skin cancer in the world associated with an older patient population and chronic diseases associated with poor healing. This is a unique population in a unique setting of a humid tropical climate which likely contributes to higher infection rates and graft failure.

Strengths and Limitations

Study Strengths

- Practical question, clinically relevant to surgical management of skin cancer
- Recruitment of clinicians and patients feasible
- Independent outcome assessor will assess photographs of all wounds
- Outcomes include clinical measurements, patient reported measures and hospital system measures

Study Limitations

- Clinical outcome assessors and patients cannot be blinded
- Assessment of graft take has an element of subjectivity
Introduction

The first use of Fibrin written in the literature was in Germany as a hemostatic, published in 1909 [1, 2]. When introduced to a wound with Thrombin, Factor XIII and Calcium it mimics the final events in the clotting cascade, turning fibrinogen into fibrin [3-5]. Originally spun from plasma intraoperatively, commercial preparations of Fibrin glue are now available which produce high concentrations of fibrin and can be used as an adhesive [6, 7]. Fibrin glue has been investigated for use in skin grafts relating to burns and shown no inferiority to staples/sutures in terms of wound closure [8]. Specifically, fibrin glue adheres the entire surface of the graft (figure 1) to the site and significantly reduces the formation of haematoma or seroma immediately post-op which commonly results in graft failure [9]. Studies have also shown less of a requirement for dressings to ensure close adherence of the graft, better haemostasis and less contraction of scar tissue for various uses of skin grafts [8-10]. Skin graft survival is dependent on vascularisation of the graft which usually begins after a 2-3 day period. During this initial period poor adherence or hematoma/seroma formation can disrupt further vascularisation and lead to graft failure. Formation of a hematoma/seroma is the most common cause for graft failure but issues with the graft recipient site such as poor vascularity, infection and inflammation can lead to graft failure [9]. Grafts over mobile sites (such as joints) can break down due to shearing forces. Also after the graft heals, the site can contract leading to aesthetic defects or functional defects where range of motion is reduced [6].

In Australia, and particularly Far North Queensland, skin cancers are a common phenomenon and many patients have cancers which are sizeable enough, to require grafting after resection for adequate wound closure [10]. This is particularly true of melanoma patients where the surgical margins required range from one centimetre upwards [11]. This results in an area of skin loss usually at least 3cm across which in the taught skin of extremities cannot be primarily closed. Many of these patients are elderly and may have diseases which impair wound healing. One of the common sites for skin cancer is the lower leg, which is particularly prone to poor healing in the presence of vascular risk factors [12] Previous studies have not addressed the use of fibrin glue in skin cancer resections nor in elderly patients and patients with vascular risk factors. Fibrin glue has been investigated for use in other difficult to graft situations such as infected sites, mobile skin areas and difficult to graft areas with good results [13-17]. These are all areas which can contribute to skin graft failure. It is possible that fibrin glue can increase graft take in patients who have vascular issues as it has been shown that increased fibrin decreases likelihood of graft failure and can induce angiogenesis [18]. If it can be shown to be beneficial in skin cancer patients (particularly the elderly and vasculopathic patients) and significantly decrease operative time and required operative follow up (i.e. for suture/staple removal) it may become a viable alternative to sutures. This could potentially change the management of skin grafts to become quicker, easier, less painful for patients and require less follow up.

There have been no clinical trials looking at the use of fibrin glue for skin grafts in skin cancer to date. There have been few trials of reasonable size looking at the use of fibrin glue in skin grafts for burns. These trials have shown apparent benefits in using fibrin glue, and it may be an effective way to improve graft take. Currently the accepted standard of care would be use of any of these techniques, however the use of glue is less common. This research seeks to provide a better evidence base to justify its use in clinical practice.

Methods and Analysis

Study Centre
This study will be conducted in one public and one private hospital in Townsville, Queensland. (Latitude 19.2590° S) Townsville is a regional centre with a population of approximately 200,000 [19] with only these two hospitals. Members of the study team have conducted multiple randomised controlled trials (RCTs) on skin excisions in the northern Queensland region. [20-22]

Study Design

This is a prospective Randomized controlled clinical trial (RCT). The intervention group will have grafts secured with fibrin glue (figure 1). The normal treatment control group will have grafts secured with sutures or staples. These methods apply in both public and private hospital settings. Data will be collected over a 24 month period. The study will be conducted in accordance with the CONSORT statement. Clinical Trial Protocol version 5 dated 22/10/19.

Intervention

The fibrin glue being used in this study is already in clinical use under the brand name ARTISS. It consists of two syringes, each containing human plasma derived coagulation factors which when mixed together start the coagulation process and form a clot. It has had TGA approval since 2010.

Recruitment of Study Participants

Patients will be recruited in the process of booking for surgery. Potential patients will be identified in two places: at surgical clinics and during the booking process for surgery. At surgical clinics patients who are undergoing skin grafts for skin cancer will be asked by their assessing clinician if they could be assessed for suitability by the inclusion criteria. If the patient declines then no further action is required. If the patient accepts, clinicians will check that they fit the inclusion criteria and give the patient an information sheet on the study, along with a consent form (Appendix 1). Informed consent will be discussed by the recruiting clinician.

Randomization

Randomisation will be performed at the level of the patient with an allocation ratio of 1:1. A computer generated random number table will create random numbers in blocks of 2 or 4 and block size will be randomised. The patient allocation will be provided in opaque sealed, tamperproof envelopes. Patients and clinicians will only be aware of the treatment allocation after the patient has been recruited into the trial. Blinding of the patient and the treating clinician to the intervention will not be possible, however the outcome assessor will be blinded to treatment allocation.

Inclusion Criteria

All patients presenting to surgical clinics requiring skin grafting will be potential participants. They will be assessed to see if they meet the following inclusion criteria:

- Will be undergoing surgery at one of the trial centres
- Have any histological type of skin cancer
- Age \( \geq \) 18 years

Exclusion Criteria

The exclusion criteria for this study are:

- Adverse reaction to the product
b) Hypersensitivity to bovine protein

c) Skin grafts on digits or genitalia

d) Pregnancy

e) Not cognitively intact to consent to participation

f) Known immunodeficiency (HIV, Leukemia, etc), or haemolytic anaemia

g) Chronic malnourishment

Surgical and Wound Protocol

The surgical and wound management protocol is to standardise management across the study arms and is modelled on similar protocols as well as in consultation with participating clinicians.[8, 23] Aside from the study interventions of sutures, staples or glue there will be standardisation of antisepsis and dressings, with patients receiving standard instructions and wound care.

Outcome Measures

The primary outcome of graft take will be compared based on review at 1 month post operatively, including photographic data and reported wound healing and graft take. Secondary outcomes will include graft take in patients with vascular disease, reported pain post dressing change scores and operative time. Outcome assessors at the time of clinical assessment included surgical medical practitioners or nursing staff with specific wound management skills. Although outcome assessors are not told allocations, due to the nature of sutures or staples being present in the wound at some points of assessment, it may be evident to clinical outcome assessors. Therefore independent blinded outcome assessors will be given photographs to estimate graft take.

Secondary outcome measures include pain on dressing changes and operative time.

Definitions

Graft take is defined as wound healing over grafted areas within the period of weeks after the skin graft procedure, rather than healing via secondary intention and granulation tissue in a prolonged period. This will be assessed both clinically and photographically to reduce inter observer variability.

Pain on dressing change is a patient reported outcome where patients will indicate on a Wong-Baker pain faces chart their pain out of ten. Operative time is defined as the time from first incision of the lesion until final dressing placement over the wound.

Data Collection

Patient characteristics:

When patients are recruited to the study they will fill out a simple questionnaire with their gender, age, and a targeted medical history to assess vascular risk factors.

Operative Data:

Operative time will be recorded for all procedures, as well as graft site and size.

Post-operative Data:

At one week follow up, patients will be asked to rate their post procedure and dressing change pain on a pain scale. Incidence of post-operative haematoma and seroma will be noted.
At one month follow up, blinded assessors will assess graft take or rejection and photos will be taken for independent validation. Surgical site infections will be noted at any time post operatively.

An adverse event would be an outcome not expected in the usual peri-operative or post-operative course of the patient which are related to the use of fibrin glue. The analysis from the Therapeutic Goods Administration in 2010 determined that none of the adverse effects noted in the trial were as a result of the fibrin glue and there were no significant safety issues. A literature search of Medline and Embase looking for papers with the terms ‘tissue adhesive’ and related terms with ‘adverse effect’ and related terms found a total 589 papers. Out of all of these papers, only four cases of hypersensitivity were noted, with two cases of anaphylaxis [24]. Three cases noted adverse events as a result of incorrect application of glue (air embolus, subcutaneous emphysema and incidental adhesion to surrounding structures) [25-27]. Patients with a hypersensitivity to bovine protein will be excluded from the trial as a precaution. Also all surgeons administering the glue have experience and knowledge in the proper application. If any adverse events were to occur then they would be discussed with the chair of the steering committee who would determine if an extra meeting of the committee would be required and notify the data safety monitoring committee and the human research and ethics committee. A logbook of adverse effects would also be kept, including those which are not related to fibrin glue.

For data safety management, patient data will be collected in a de-identified format, with a potential for re-identification for situations of adverse events. The re-identification code will be password protected, as will the data collected and will only be able to be accessed by the principal investigator and co-investigators.

Due to the size of the trial a trial management group consisting of both clinicians and researchers was established. One independent person was deemed to be sufficient as an independent data-monitor who has no affiliation with the management group. The positive stopping rule for the trial management group for each interim analysis is 25% recruited (p<0.0000001); 50% recruited (p<0.000001); 75% recruited (p<0.00001). If patients with fibrin glue show a worse rate of graft take, the negative stopping rule is p<0.05.

**Sample Size Calculation**

A two tailed analysis assuming a power of 0.80 and alpha of 0.05 gave 334 patients in total with 167 in each group [28]. It would likely take approximately one to two years to recruit enough patients for this study. Sample size was determined by power testing with similar papers, one of which compared approximately 300 cases of split skin graft [8]. In this paper at day 28 approximately 68% of participants had 100% take of skin graft in the group using sutures or staples rather than fibrin glue and a 10% difference was considered significant. An estimate of graft take in the general population patients would be drawn from was roughly estimated as 50% and a clinically significant difference was determined to be 15% for this study.

**Data Analysis**

Graft take will be compared based on review at 1 month post operatively, including photographic data and reported wound healing and graft take. Groups will be compared using a two proportion z-test. A sub group analysis on the impact of vascular risk factors will be performed, as well as on haematoma and seroma formation, although the study is not powered for this analysis.

Data will be analysed using statistical software StataSE 16 [29]. Demographic data will be presented as percentages. Continuous variables will be tested for normality and based on the outcome of the
test, parametric or non-parametric analyses of the data will be undertaken. Z-test analysis to compare two proportions will be used for analysis of graft take. A p value of <0.05 will be considered statistically significant. The data may also be used in aggregate to conduct a cost effectiveness analysis.

**Potential Problems**

Based on the number of patients seen in both hospitals presently for skin cancer excisions, we believe that recruitment of adequate numbers is feasible. However, if we fail to recruit enough patients, other north Queensland hospital sites may be approached and invited to participate.

Patients currently attend for wound redressing appointments initially at the hospital where their operation is performed. Subsequent to these initial reviews if further dressings are required and the patient has a significant travel time then community dressings may be organised. Given that most patients already receive their wound care within the hospital they will have their post operative outcomes assessed at these appointments.

**Patient and Public Involvement**

Patient and public representatives were present on the Ethics Committee reviewing the design and research. Results from this trial will be reported publicly.

**Ethics and Dissemination**

**Ethical Considerations**

We do not expect the intervention in this study to place participants at any significant risk of harm, as current evidence demonstrates at least equivalent outcomes for the fibrin glue intervention [30]. Protocol amendments will be communicated to all relevant parties electronically.

To assure privacy and confidentiality, all data spreadsheets and consent forms will be kept in a locked cupboard throughout the trial, then transferred to a locked safe at the conclusion of the trial, where they will be kept for 15 years. Electronic copies of any forms will be kept on encrypted hard drives and patients will be deidentified in all data collection.

**Dissemination**

Once adequate data collection has been attained, dissemination of findings will occur via conference presentations and scientific journals. The researchers will also aim to present their findings at clinical meetings in the north Queensland area where there is a potential impact on surgical practice patterns.

**Discussion**

The purpose of this trial is the evaluation of a new surgical technology in a different patient population to past research in this area. In a systematic review of the literature, only two studies with a total n of 54 out of 15 randomised controlled trials with a cumulative n of 594 included patients with skin cancer at all. This is clearly an area where further work is required and it is particularly relevant to the population in regional North Queensland. In epidemiologic research tracking back a number of decades, Queensland, and in particular North Queensland where
Townsville is situated, has been noted as the region with the highest incidence of skin cancer in the world [31-34]. The most recent of these notes a strong predilection towards elderly males and echoes the finding that the high rates of skin cancer likely relate to phenotypic predisposition (low Fitzpatrick skin type) and environmental exposures (UV radiation) [34]. Age predisposes to increased vascular disease or diabetes which impairs wound healing [35, 36]. As well as increased incidence of skin cancer, and wound healing may be affected by the tropical climate in Townsville, where mean maximum daily temperature ranges from 25.2 to 31.6 degrees Celsius and mean relative humidity between 50-70% throughout the year [37]. These weather patterns have been theorised to increase risk of infection due to humidity causing damp dressings which are an ideal environment for bacterial ingress and the authors’ clinical experience supports this [38].

Therefore, it is a phase 4 clinical trial with a focus on pragmatic outcomes and to achieve this has a simple design. A pragmatic trial design is most appropriate to evaluate the broad applicability of this intervention across many populations. Controlling all patient factors would also limit the ability of this trial to answer the question of whether fibrin glue is superior in patients who do not have optimal wound healing. There are a few potential issues with the trial design, a major one being blinding of the surgeons utilising the fibrin glue. This is an issue evident in the use of any new surgical technology, as is the blinding of patients once they are able to see their wound during dressing changes. We expect that this trial, like many, may have issues in recruitment however the patient pool is quite large and hopefully reasonable endpoints can be made. Although blinding is not perfect, the use of sealed opaque envelopes and a specific order for allocation will help reduce bias in allocation.

One issue which has been noted in other trials is the heterogeneity of chosen endpoints. Selection of specific endpoints for reporting in the literature is a potential issue, as is usage of different methods to measure endpoints. This may reflect differences in opinions as to which outcomes are important to measure but makes cross study comparisons difficult. For this study we have chosen a number of outcomes which reflect clinical measurements, patient reported measures and hospital system measures. We hope that this adequately captures the many levels of decision making involved in choosing to use new surgical technology.
### WHO Trial Registration Data Set

| WHO Trial Registration Data Set | Australian New Zealand Clinical Trials Registry  
|--------------------------------| ACTRN12618000484246  
| Primary registry and trial identifying number |  
| Date of registration in primary registry | 04 April 2018  
| Secondary identifying numbers | Nil  
| Source(s) of monetary or material support | Townsville University Hospital Grant  
| Primary sponsor | Townsville University Hospital Grant  
| Secondary sponsor(s) | Nil  
| Contact for public queries | EP, MBBS, MPH (ekta.paw@my.jcu.edu.au)  
| Contact for scientific queries | EP, MBBS, MPH (ekta.paw@my.jcu.edu.au)  
| Public title | Determining the Efficacy of Fibrin Glue in Skin grafts for Skin cancer (FiGSS): Open randomised clinical trial  
| Scientific title | Determining the Efficacy of Fibrin Glue in Skin grafts for Skin cancer (FiGSS): Open randomised clinical trial  
| Countries of recruitment | Australia  
| Health condition(s) or problem(s) studied | Skin cancer, Skin Graft Failure  
| Intervention(s) | Active comparator: Topical Fibrin Glue  
| Placebo comparator: Suture or Staple Fixation  
| Ages eligible for study: ≥18 years  
| Sexes eligible for study: both  
| Accepts healthy volunteers: no  
| Inclusion criteria:  
| a) Will be undergoing surgery at one of the trial centres  
| b) Have any histological type of skin cancer  
| Key inclusion and exclusion criteria | Exclusion criteria: a) Adverse reaction to the product (Fibrin Glue)  
| b) Hypersensitivity to bovine protein  
| c) Skin grafts on digits or genitalia  
| d) Pregnancy  
| e) Not cognitively intact to consent to participation  
| f) Known immunodeficiency (HIV, Leukemia, etc), or haemolytic anaemia  
| g) Chronic malnourishment  
| Study type | Interventional  
| Allocation: randomized intervention model. Masking: open with blinded outcome assessors  
| Primary purpose: treatment  
| Phase IV  

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
Date of first enrolment | April 2018
---|---
Target sample size | 334
Recruitment status | Recruiting
Primary outcome(s) | Graft take based on wound healing at one month
Key secondary outcomes | Pain on dressing changes and operative time.

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The authors thank Ronny Gunnarsson for his guidance in trial design. We used the SPIRIT checklist when writing our report [39].

Competing Interests

None declared.

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Ethics Approval

This project has been reviewed and approved by the Townsville University Hospital Human Research Ethics Committee. HREC Reference number: HREC/17/QTHS/196

Author Contributions

EP conceived of the study idea and developed the protocol and study design. VV CH and MZ contributed to the development of the study design and protocol with VV also assisting with sample size calculation and statistics. All Authors contributed to the drafting of the manuscript.

References

1. Bergel, S., *Ueber Wirkungen des Fibrins*. Dtsch Med Wochenschr, 1909. **35**(15): p. 663-665.
2. Spotnitz, W.D., *Fibrin Sealant: Past, Present, and Future: A Brief Review*. World Journal of Surgery, 2010. **34**(4): p. 632-634.
3. Currie, L., J. Sharpe, and R. Martin, *The Use of Fibrin Glue in Skin Grafts and Tissue-Engineered Skin Replacements: A Review*. Plastic and Reconstructive Surgery, 2001. **108**(6): p. 1713-1726.
4. Brennan, M., *Fibrin Glue*. Blood Reviews, 1991. **5**: p. 240-244.
5. Rousou, J., R. Engelman, and R. Breyer, *Fibrin Glue: An Effective Hemostatic Agent for Nonsutureable Intraoperative Bleeding*. The Annals of Thoracic Surgery, 1984. **38**(4): p. 409-410.
6. Kjaergard, H.K. and U.S. Weis-Fogh, *Important factors influencing the strength of autologous fibrin glue; the fibrin concentration and reaction time--comparison of strength with commercial fibrin glue*. Eur Surg Res, 1994. **26**(5): p. 273-6.
7. Buckley, R., et al., *A Simple Preparation of Autologous Fibrin Glue for Skin-Graft Fixation*. Plastic and Reconstructive Surgery, 1999. **103**(1): p. 202-206.

8. Foster, K., et al., *Efficacy and safety of a fibrin sealant for adherence of autologous skin grafts to burn wounds: results of a phase 3 clinical study*. J Burn Care Res, 2008. **29**(2): p. 293-303.

9. Teh, B., *Why do skin grafts fail?* Plastic and Reconstructive Surgery, 1979. **63**(3): p. 324-332.

10. Wilkinson, D., D. Askew, and A. Dixon, *Skin cancer clinics in Australia: workload profile and performance indicators from an analysis of billing data*. Medical Journal of Australia, 2006. **184**(4): p. 162.

11. Sladden, M.J., et al., *Surgical excision margins for primary cutaneous melanoma*. Cochrane Database of Systematic Reviews, 2009(4).

12. Bishop, J.N., et al., *The prevention, diagnosis, referral and management of melanoma of the skin: concise guidelines*. Clinical medicine (London, England), 2007. **7**(3): p. 283-290.

13. Boeckx, W., et al., *Fibrin glue in the treatment of dorsal hand burns*. Burns, 1992. **18**(5): p. 395-400.

14. Shetty, S., M. Shetty, and A. Colaco, *Can Use of fibrin glue in Peridontal Flap Surgery be an alternative to suturing? - A Review*. International Journal of Advanced Research, 2015. **3**(9): p. 1573-1575.

15. Lilius, P., *Fibrin Adhesive: Its Use in Selected Skin Grafting*. Scandinavian Journal of Plastic and Reconstructive Surgery, 2009. **21**(3): p. 245-248.

16. Vedung, S. and A. Hedlund, *Fibrin Glue: Its Use for Skin Grafting of Contaminated Burn Wounds in Areas Difficult to Immobilize*. Journal of Burn Care & Rehabilitation, 1993. **14**(3): p. 356-358.

17. Jabs, A.D., et al., *The Effect of Fibrin Glue on Skin Grafts in Infected Sites*. Plastic and Reconstructive Surgery, 1992. **89**(2): p. 268-271.

18. Dvorak, H.F., et al., *Fibrin Containing Gels Induce Angiogenesis*. Laboratory Investigation, 1987. **57**(6): p. 673-686.

19. Australian Bureau of Statistics. *2016 Census of Population and Housing*. Australian Census 2016 [cited 2021 July 19]; Available from: https://quickstats.censusdata.abs.gov.au/census_services/getproduct/census/2016/quickstat/036.

20. Gorges, H., L. Hall, and C. Heal, *Feasibility Study for a Randomised Controlled Trial for the Topical Treatment of Impetigo in Australian General Practice*. Tropical Medicine and Infectious Disease, 2021. **6**: p. 197.

21. Heal, C., et al., *Building a bridge from the swamp to the ivory tower: Conducting randomised controlled trials in general practice*. Aust J Gen Pract, 2018. **47**(3): p. 153-157.

22. Ediriweera, Y., et al., *A study protocol for a randomised controlled trial of ice to reduce the pain of immunisation: The ICE trial*. Australian Journal of General Practice, 2022. **51**: p. 173-177.

23. Hierner, R., et al., *Skin grafting and wound healing—the “dermato-plastic team approach”*. Clinics in Dermatology, 2005. **23**(4): p. 343-352.

24. Jankowski, R., et al., *[Hypersensitivity accidents to thrombin following the use of biological glues]*. Ann Otolaryngol Chir Cervicofac, 1992. **109**(2): p. 95-9.
25. Felema, G.G., et al., *Venous air embolism from Tisseel use during endoscopic cranial vault remodeling for craniostynostosis repair: a case report*. Paediatr Anaesth, 2013. 23(8): p. 754-6.

26. Matsuse, S., A. Maruyama, and Y. Hara, *Nitrogenous subcutaneous emphysema caused by spray application of fibrin glue during retroperitoneal laparoscopic surgery*. Journal of Anesthesia, 2011. 25(3): p. 426.

27. Ohta, M., et al., *Complication caused by use of fibrin glue in vessel transposition for trigeminal neuralgia*. Neurol Med Chir (Tokyo), 2008. 48(1): p. 30-2.

28. Faul, F., et al., *G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behavior Research Methods, 2007. 39: p. 175-191.

29. StataCorp, *Stata Statistical Software: Release 16*. 2019, StataCorp LP: College Station, TX.

30. Paw, E., et al., *Effectiveness of fibrin glue in skin graft survival: A systematic review and meta-analysis*. Annals of medicine and surgery (2012), 2020. 56: p. 48-55.

31. Stenbeck, K.D., et al., *Patterns of treated non-melanoma skin cancer in Queensland — the region with the highest incidence rates in the world*. Medical Journal of Australia, 1990. 153(9): p. 511-515.

32. Silverstone, H. and J.H.A. Searle, *The Epidemiology of Skin Cancer in Queensland: The Influence of Phenotype and Environment*. British Journal of Cancer, 1970. 24(2): p. 235-252.

33. Diepgen, T.L. and V. Mahler, *The epidemiology of skin cancer*. British Journal of Dermatology, 2002. 146(s61): p. 1-6.

34. Raasch, B.A. and P.G. Buettner, *Multiple nonmelanoma skin cancer in an exposed Australian population*. International Journal of Dermatology, 2002. 41(10): p. 652-658.

35. Thomas, D.R., *Age-Related Changes in Wound Healing*. Drugs & Aging, 2001. 18(8): p. 607-620.

36. Vos, T., et al., *Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013*. The Lancet, 2015. 386(9995): p. 743-800.

37. Commonwealth of Australia Bureau of Meteorology. *Climate statistics for Australian locations Townsville*. Climate statistics for Australian locations 2022 [cited 2022 26 April]; Available from: http://www.bom.gov.au/climate/averages/tables/cw_032040_All.shtml.

38. Heal, C., et al., *Can sutures get wet? Prospective randomised controlled trial of wound management in general practice*. BMJ, 2006. 332(7549): p. 1053.

39. Chan, A.W., et al., *SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials*. Bmj, 2013. 346: p. e7586.
Figure Legend

Figure 1: A graphic to demonstrate the differences in skin graft fixation between sutures and staples (left) and fibrin glue (right).

Appendix 1 Example Participant Information and Consent Form
Patient/participant information sheet and consent form

Protocol name: Fibrin Glue in Skin Grafts for Skin Cancer (FiGSS)
Investigators: Principal investigator Ekta Paw BSc MBBS

1 Introduction

You are invited to take part in this research project. This is because you have a skin cancer which requires a skin graft. The research project is to compare different ways to attach skin grafts.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don’t understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don’t wish to take part, you don’t have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

- Understand what you have read
- Consent to take part in the research project
- Consent to have the tests and treatments that are described
- Consent to the use of your personal and health information as described.

2 What is the purpose of this research?

Skin cancer is incredibly common in North Queensland. Many people need large sections of skin removed to treat their cancer, and skin grafts to close their wounds. Instead of attaching these grafts with stitches or staples, a newer method is to use Fibrin glue, which is made from a protein found in humans which stops bleeding. By sticking to the whole surface of the graft, it is thought that Fibrin glue may improve healing. It may have an important effect in patients who are more likely to have graft failure, such as those with poor circulation, smokers, or the elderly.

Fibrin glue has been approved by the Australian Federal Government for use in attaching skin grafts for a number of years. There is research already on using it for burns, but not in skin cancer.
The results of this research will be used by the study doctor Ekta Paw to obtain a Masters of Philosophy degree.

3 What does participation in this research involve?

Participation in this project does not change your surgery. For some patients not participating in the trial we may also use the glue, as it is already part of usual care.

If there are no reasons you cannot participate in the study, you will be randomised to either: staples and stitches to attach your graft; or to the group which has fibrin glue to attach the graft. Your surgery will proceed as normal and your follow up appointments will be the same as normal (one week and one month). The only difference is that we will ask some questions about your medical history; your post-operative pain; and we will take photographs of your graft. The photographs will not include anything identifiable, and will only be seen by researchers to assess how well your wound has healed.

This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids study doctors or participants jumping to conclusions. Safety of the research will be monitored by a data safety management committee. There is also a study steering committee who will continually monitor progress and any unexpected events as they occur.

There are no additional costs associated with participating in this research project, nor will you be paid.

4 What do I have to do?

You will have to attend your surgery date as per usual, and your follow up appointments which are the same as if you were not participating in the study. It is important you attend these appointments on time as it will help assess the effectiveness of the glue. You can continue all your regular medications.

5 Other relevant information about the research project

There will be 334 patients participating in this study, of which half will have the glue used, and half will have stitches or staples used. There are two hospitals in Townsville involved.

6 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage. If you do decide...
to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

7 **What are the alternatives to participation?**

If you don’t participate, your surgery will occur as usual, with the usual follow up. It is possible you may still have Fibrin glue used for your skin graft as it is part of the current standard of care.

8 **What are the possible benefits of taking part?**

We cannot guarantee or promise that you will receive any benefits from this research; however, possible benefits may include better healing of skin graft, less risk of infection, faster surgery and less pain after surgery. By taking part you may have an increase in the observation of your wounds and because of this problems or issues may be picked up faster. Taking part will enable doctors to know if this glue is truly better or not. If the glue is shown to improve outcomes, future patients may have better healing, less pain, less infections and need to attend hospital less often after having skin grafts.

9 **What are the possible risks and disadvantages of taking part?**

While Fibrin glue has been approved by the Australian Federal Government, there have been a small number of adverse outcomes reported which have been associated with its use. These have mainly related to hypersensitivity reactions to the proteins. It is for this reason that we will not allow people who have a known allergy to bovine protein to participate in this study. However, it is possible you may have an allergy without knowing about it previously. Allergy reactions can range from itchiness and redness, to difficulty breathing and a drop in blood pressure. While this is a very rare occurrence, if it does occur it will be within a very short time of exposure to the allergen (Fibrin glue), and you will be closely monitored during and after your surgery for any signs of this so it can be treated quickly.

10 **What if I withdraw from this research project?**

You are welcome to withdraw from this research project at any time if you no longer wish to be a participant. Your surgery and follow up will go ahead as usual, with no change to the timing or quality of your care. Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with Townsville Hospital/Mater Health Services North Queensland.

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the
research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the sponsor up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

11 Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as:

- Unacceptable side effects
- The treatment being shown not to be effective
- The treatment being shown to work and not need further testing

12 What will happen to information about me?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project will be that can identify you will remain confidential. Data will be kept in a form which does not identify you, but in case we need to re-identify a participant for medical reasons there will be a code. This code will be kept securely in a password protected electronic format which can only be accessed by the researchers involved in this study. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law. Data will be kept securely for 15 years following completion of the study as per James Cook University guidelines.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form you agree to the study team accessing health records if they are relevant to your participation in this research project.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission. Data will only be presented as numerical results with no identification of individual participants.
13 Complaints and compensation

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

14 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of Townsville Hospital.

This project will be carried out according to the National Statement on Ethical Conduct in Human Research (2007). This statement has been developed to protect the interests of people who agree to participate in human research studies.

15 Further information and who to contact

The person you may need to contact will depend on the nature of your query. If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor on 4433 1111 or any of the following people: Dr Mark Zonta, Dr Venkat Vangaveti.

Research Contact Person:
Name: Dr Ekta Paw
Position: Principal House Officer, General Surgery
Phone: 4433 1111
Email: ekta.paw@health.qld.gov.au

This project has been reviewed and approved by the Townsville Hospital and Health Service Human Research Ethics Committee. For concerns relating the conduct of this project contact:
HREC Chairperson
Phone: 07 4433 1440
Email: TSV-Ethics-Committee@health.qld.gov.au
PATIENT/PARTICIPANT CONSENT FORM

PROTOCOL NAME: Fibrin Glue in Skin Grafts for Skin Cancer (FiGSS)

INVESTIGATORS: Principal investigator Ekta Paw BSc MBBS

1. The nature and purpose of the research project has been explained to me. I understand it and acknowledge that taking part in this study is voluntary.

2. I have been given an Information Sheet which explains the purpose of the study, the possible benefits, and the possible risks.

3. I understand that I may not directly benefit from taking part in the trial.

4. I understand that, while information gained during the study may be published, I will not be identified and my personal results will remain confidential.

5. I understand that I can withdraw from the study at any stage and that it will not affect my medical care, now or in the future.

6. I have had the opportunity to discuss taking part in this investigation with a family member or friend.

NAME OF PARTICIPANT: ____________________________

SIGNATURE: ____________________________

DATED: ____________________________

I certify that I have explained the study to the patient/volunteer and consider that he/she understands what is involved.

NAME OF PRINCIPAL INVESTIGATOR: Dr Ekta Paw

SIGNATURE: ____________________________
Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

**Instructions to authors**

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Götzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

| Reporting Item                                      | Page Number |
|-----------------------------------------------------|-------------|
| Administrative information                          |             |
| Title                                                | #1          |
| Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1           |
| Trial registration                                   | #2a         |
| Trial identifier and registry name. If not yet registered, name of intended registry | 2           |
| Trial registration: data set                         | #2b         |
| All items from the World Health Organization Trial Registration Data Set | 10          |
| Protocol version                                     | #3          |
| Date and version identifier                          | 4           |
| Funding                                              | #4          |
| Sources and types of financial, material, and other support | 10          |
| Roles and responsibilities: contributorship          | #5a         |
| Names, affiliations, and roles of protocol contributors | 1           |
| Roles and responsibilities: sponsor contact information |
|--------------------------------------------------------|
| #5b Name and contact information for the trial sponsor |

| Roles and responsibilities: sponsor and funder |
|-----------------------------------------------|
| #5c Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities |

| Roles and responsibilities: committees |
|---------------------------------------|
| #5d Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) |

| Introduction |
|--------------|
| #6a Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention |

| Background and rationale: choice of comparators |
|-----------------------------------------------|
| #6b Explanation for choice of comparators |

| Objectives |
|------------|
| #7 Specific objectives or hypotheses |

| Trial design |
|-------------|
| #8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory) |

| Methods: Participants, interventions, and outcomes |
|-------------------------------------------------|
| Study setting |
| #9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained |

| Eligibility criteria |
|----------------------|
| #10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will... |
perform the interventions (eg, surgeons, psychotherapists)

Interventions: #11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered

Interventions: #11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)

Interventions: #11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)

Interventions: #11d Relevant concomitant care and interventions that are permitted or prohibited during the trial

Outcomes #12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended

Participant timeline #13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)

Sample size #14 Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations

Recruitment #15 Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation: sequence generation #16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism #16b
Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned

Allocation: implementation #16c
Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions

Blinding (masking) #17a
Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how

Blinding (masking): emergency unblinding #17b
If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial

Methods: Data collection, management, and analysis

Data collection plan #18a
Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol

Data collection plan: retention #18b
Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols

Data management #19
Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol

Statistics: outcomes #20a
Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol

Statistics: additional analyses #20b
Methods for any additional analyses (eg, subgroup and adjusted analyses)
Statistics: analysis population and missing data

Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

Methods: Monitoring

Data monitoring: formal committee

Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

Data monitoring: interim analysis

Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial

Harms

Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct

Auditing

Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval

Plans for seeking research ethics committee / institutional review board (REC / IRB) approval

Protocol amendments

Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)

Consent or assent

Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)

Consent or assent: ancillary studies

Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

Confidentiality

How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests #28 Financial and other competing interests for principal investigators for the overall trial and each study site

Data access #29 Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators

Ancillary and post trial care #30 Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation

Dissemination policy: trial results #31a Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions

Dissemination policy: authorship #31b Authorship eligibility guidelines and any intended use of professional writers

Dissemination policy: reproducible research #31c Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials #32 Model consent form and other related documentation given to participants and authorised surrogates

Biological specimens #33 Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

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# Protocol for an open randomised controlled trial investigating Fibrin Glue in Skin grafts for Skin cancer (FiGSS)

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Protocol for an open randomised controlled trial investigating Fibrin Glue in Skin grafts for Skin cancer (FiGSS)

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Key words
Fibrin Tissue Adhesive, Skin Transplantation, Skin Neoplasms, Prospective Studies

Word Count
3230
Abstract

Introduction

Skin cancer is a common disease in the tropics, and oncologic resection typically requires reconstruction with skin grafts. Fibrin glue, initially established as a haemostatic agent, has been studied extensively as an adhesive for skin grafts in burns. This study aims to investigate the use of fibrin as an adhesive for split skin grafts in skin cancers.

Methods and Analysis

The study design is a prospective randomised controlled trial with the aim of investigating the impact of two different methods of split skin graft fixation. The intervention of fibrin glue will be compared to the control of staples or sutures. The trial will be conducted at two sites, a public and private hospital in Townsville, Australia over a 24 month period with 334 participants to be recruited. Consecutive patients presenting for skin excisions and grafting will be eligible to participate. Randomisation will be on the level of the patient. The primary outcome is graft take based on wound healing at one month. Secondary outcomes will be pain on dressing changes and operative time.

Ethics and Dissemination

The study has been approved by The Townsville University Hospital Human Research Ethics Committee (HREC). Findings will be disseminated in conference presentations and journals and through online electronic media.

Registration Details

Registered on Australian New Zealand Clinical Trials Registry ACTRN12618000484246

Strengths and Limitations

Study Strengths

- Practical question, clinically relevant to surgical management of skin cancer
- Blinded independent outcome assessor will assess photographs of all wounds
- Outcomes include clinical measurements, patient reported measures and hospital system measures

Study Limitations

- Surgeons and patients cannot be blinded
- Assessment of graft take has an element of subjectivity

Introduction

The first described use of intraoperative Fibrin was in 1909 where German surgeons used it as a hemostatic [1, 2]. When introduced to a wound with Thrombin, Factor XIII and Calcium it mimics the final events in the clotting cascade, cleaving fibrinogen to fibrin [3-5]. Fibrin was originally spun from patient plasma intraoperatively, but now commercial preparations of Fibrin glue are now available with high concentrations of fibrin that can be used as an adhesive [6, 7]. Fibrin glue has been
investigated for use in skin grafts relating to burns and shown no inferiority to staples/sutures in terms of wound closure [8-11]. Specifically, fibrin glue adheres the entire surface of the graft to the wound bed (figure 1) and significantly reduces the formation of haematoma or seroma immediately post operatively[10]. Studies have also shown use of fibrin glue results in a decreased requirement for dressings to ensure close adherence of the graft; better haemostasis; and less contraction of scar tissue [8-10]. Skin graft survival is dependent on vascularisation of the graft which usually begins after a two to three day period. During this initial period poor adherence or hematoma/seroma formation can disrupt further vascularisation and reduce graft imbibition of oxygen and nutrients from the graft bed[10, 12]. Formation of a hematoma/seroma is the most common cause for graft failure[10, 12]. Issues with the graft recipient site such as poor vascularity, infection, inflammation or shearing forces over mobile skin areas can also lead to graft failure[10]. After wound closure, the site can also contract leading to aesthetic defects or functional defects due to reduced range of motion [6].

In Australia, and particularly Far North Queensland, skin cancers are incredibly common and many patients have cancers which are sizeable enough to require grafting after resection for adequate wound closure [13]. This is particularly true of melanoma patients where the surgical margins range from one centimetre upwards [14]. This results in an area of skin loss usually at least three centimetres across which in the taught skin of extremities cannot be primarily closed. Many of these patients are elderly and may have diseases which impair wound healing. One of the common sites for skin cancer is the lower leg, which is particularly prone to poor healing in the presence of vascular risk factors [15] Previous studies have not addressed the use of fibrin glue in skin cancer resections nor in elderly patients and patients with vascular risk factors. Fibrin glue has been investigated for use in other difficult to graft situations such as infected sites, mobile skin areas and difficult to graft areas with good results [8, 16-19]. These are all areas which can contribute to skin graft failure. It is possible that fibrin glue can increase graft take in patients who have vascular issues as it has been shown that increased fibrin decreases likelihood of graft failure and can induce angiogenesis [20]. If it can be shown to be beneficial in skin cancer patients (particularly elderly and vasculopathic patients) and significantly decrease operative time and required operative follow up it may be a viable alternative to sutures. This could potentially change the management of skin grafts to become quicker, easier, less painful for patients and require less follow up.

There have been no clinical trials looking at the use of fibrin glue for skin grafts in skin cancer to date.[11] There have been few trials of reasonable size looking at the use of fibrin glue in skin grafts for burns.[10, 11] These trials have shown apparent benefits in using fibrin glue, and it may be an effective way to improve graft take. Currently the accepted standard of care would be use of any of these techniques, however the use of glue is less common.

The objective of this study is to examine the effectiveness of fibrin glue in reconstruction of oncologic skin resection. If our research demonstrates increased effectiveness of glue it may lead to a change in behaviour which may reduce the incidence of graft failure in this patient population.

**Methods and Analysis**

**Study Centre**

This study will be conducted in Townsville, Queensland (Latitude 19.2590° S). Townsville is a regional centre with a population of approximately 200,000 [21] with only two hospitals. One hospital is government funded with the other privately funded, and patients will be recruited from both sites.
Members of the study team have conducted multiple randomised controlled trials (RCTs) on skin excisions in the northern Queensland region. [22-24]

Study Design

This is a prospective randomized controlled clinical trial (RCT). The intervention group will have grafts secured with fibrin glue across the graft bed (figure 1). The normal treatment control group will have grafts secured peripherally only with sutures or staples. These methods apply in both public and private hospital settings. Data will be collected over a 24 month period. The study will be reported in accordance with the CONSORT statement. Clinical Trial Protocol version 5 dated 22/10/19 and WHO Trial Registration Data Set provided in Table 1. We used the SPIRIT checklist when writing our report [25].

Intervention

The fibrin glue being used in this study is already in clinical use under the brand name ARTISS. It consists of two syringes, each containing human plasma derived coagulation factors which when mixed, initiate coagulation and form a clot. It has had TGA approval since 2010. This study specifically examines the effect of intraoperative application of a thin layer of fibrin glue across the entire graft bed immediately prior to the skin graft placement. This is diagrammatically represented in Figure 1.

Recruitment of Study Participants

Patients will be recruited in the process of booking for surgery. Potential patients will be identified in two places: at surgical clinics and during the booking process for surgery. Clinicians will discuss study participation with patients who are undergoing skin grafts for skin cancer. If the patient declines, then no further action is required. If the patient accepts, clinicians will check that they fit the inclusion criteria and provide an information sheet and consent form (Appendix 1). Informed consent will be discussed by the recruiting clinician.

Randomization

Randomisation will be performed at the level of the patient with an allocation ratio of 1:1. A computer generated random number table will create random numbers in blocks of 2 or 4 and block size will be randomised. The patient allocation will be provided in sequential, opaque, sealed, tamperproof envelopes. Patients and clinicians will only be aware of the treatment allocation after the patient has been recruited into the trial. Blinding of the patient and the treating clinician to the intervention will not be possible, however an independent outcome assessor will be blinded to treatment allocation.

Inclusion Criteria

All patients presenting to surgical clinics requiring skin grafting will be potential participants. They will be assessed to see if they meet the following inclusion criteria:

a) Will be undergoing surgery at one of the trial centres
b) Have any histological type of skin cancer
c) Age ≥ 18 years

Exclusion Criteria

The exclusion criteria for this study are:
Surgical and Wound Protocol

The surgical and wound management protocol is to standardise management across the study arms. This is modelled on similar protocols and in consultation with participating clinicians.[26, 27] Intraoperative application of fibrin glue includes standardised technique and timing. Dressings have been standardised at all wound sites to include a paraffin-based gauze dressing directly on the wound site, followed by foam dressing and an adhesive, non-woven fabric. Patients received standard postoperative and wound care instructions.

Outcome Measures

The primary outcome of graft take will be compared based on review at one month post operatively, including photographic data and reported wound healing and graft take. Graft healing at one week will also be examined as a secondary outcome measure. Additional secondary outcomes will include reported pain post dressing change scores and operative time. Subgroup analysis of patients who have vascular risk factors (including smoking, hypertension, diabetes, hypercholesterolaemia) or vascular disease (myocardial infarction, stroke or other vascular disease) will be performed.

Outcome assessors at the time of clinical assessment included surgical medical practitioners or nursing staff with specific wound management skills. Although outcome assessors are not told allocations, due to the nature of sutures or staples being present in the wound at some points of assessment, it may be evident to the initial outcome assessors. To mitigate this bias, independent blinded outcome assessors will be shown photographs to estimate graft take. Both assessments will be compared in the analysis.

Secondary outcome measures include pain on dressing changes, operative time and adverse events.

Definitions

Graft take is defined as wound healing over grafted areas within the period of weeks after the skin graft procedure, rather than healing via secondary intention and granulation tissue in a prolonged period. This will be assessed both clinically and photographically to reduce inter observer variability.

Pain on dressing change is a patient reported outcome where patients will indicate on a Wong-Baker pain faces chart their pain out of ten. Operative time is defined as the time from first incision of the lesion until final dressing placement over the wound.

Data Collection

Patient characteristics:
When patients are recruited to the study they will fill out a simple questionnaire with their gender, age, and a targeted medical history.

Operative Data:

Operative time will be recorded for all procedures, as well as graft site and size.

Post-operative Data:

At one week follow up, blinded assessors will assess graft take or rejection and photos will be taken for independent validation. Patients will be asked to rate their post procedure and dressing change pain on a pain scale.

At one month follow up, blinded assessors will assess graft take or rejection and photos will be taken for independent validation.

Surgical site infections and incidence of post-operative haematoma and seroma will be noted at any time post operatively.

An adverse event would be an outcome not expected in the usual peri-operative or post-operative course of the patient which are related to the use of fibrin glue. The analysis from the Therapeutic Goods Administration in 2010 determined that none of the adverse effects noted in the trial were due to the fibrin glue and there were no significant safety issues. A literature search of Medline and Embase looking for papers with the terms ‘tissue adhesive’ and related terms with ‘adverse effect’ and related terms found a total 589 papers. Out of all these papers, only four cases of hypersensitivity were noted, with two cases of anaphylaxis [28]. Three cases noted adverse events resulting from incorrect application of glue (air embolus, subcutaneous emphysema and incidental adhesion to surrounding structures) [29-31]. Patients with a hypersensitivity to bovine protein will be excluded from the trial as a precaution. Additionally, all surgeons administering the glue have experience and knowledge in the proper application. If any adverse events were to occur, then they would be discussed with the chair of the steering committee who would determine if an extra meeting of the committee would be required and notify the data safety monitoring committee and the human research and ethics committee. A logbook of adverse effects would also be kept, including those which are not related to fibrin glue.

For data safety management, patient data will be collected in a de-identified format, with a potential for re-identification for situations of adverse events. The re-identification code will be password protected, as will the data collected and will only be able to be accessed by the principal investigator and co-investigators.

Due to the size of the trial a trial management group consisting of both clinicians and researchers was established. One independent person was deemed to be sufficient as an independent data-monitor who has no affiliation with the management group. The positive stopping rule for the trial management group for each interim analysis is 25% recruited (p<0.0000001); 50% recruited (p<0.000001); 75% recruited (p<0.00001). If patients with fibrin glue show a worse rate of graft take, the negative stopping rule is p<0.05.

Sample Size Calculation

A two tailed analysis assuming a power of 0.80 and alpha of 0.05 gave 334 patients in total with 167 in each group [32]. It would likely take approximately one to two years to recruit enough patients for this study. Sample size was determined by power testing with similar papers, one of which compared approximately 300 cases of split skin graft [26]. In this paper at day 28 approximately 68%
of participants had 100% take of skin graft in the group using sutures or staples rather than fibrin glue and a 10% difference was considered significant. An estimate of graft take in the general population patients would be drawn from was roughly estimated as 50% and a clinically significant difference was determined to be 15% for this study.

Data Analysis

Graft take will be compared based on review at one week and one month post operatively, including photographic data and reported wound healing and graft take. Groups will be compared using a two proportion z-test. A subgroup analysis on the impact of vascular risk factors will be performed, as well as on haematoma and seroma formation, although the study is not powered for this analysis.

Data will be analysed using statistical software StataSE 16 [33]. Demographic data will be presented as percentages. Continuous variables will be tested for normality and based on the outcome of the test, parametric or non-parametric analyses of the data will be undertaken. Z-test analysis to compare two proportions will be used for analysis of graft take. A p value of <0.05 will be considered statistically significant. The data may also be used in aggregate to conduct a cost effectiveness analysis.

Potential Problems

Based on the number of patients seen in both hospitals presently for skin cancer excisions, we believe that recruitment of adequate numbers is feasible. However, if we fail to recruit enough patients, other north Queensland hospital sites may be approached and invited to participate.

Patients currently attend for wound redressing appointments initially at the hospital where their operation is performed. After these initial reviews if further dressings are required and the patient has a significant travel time then community dressings may be organised. Given that most patients already receive their wound care within the hospital they will have their post operative outcomes assessed at these appointments.

Patient and Public Involvement

Patient and public representatives were present on the Ethics Committee reviewing the design and research. Results from this trial will be reported publicly.

Ethics and Dissemination

Ethical Considerations

We do not expect the intervention in this study to place participants at any significant risk of harm, as current evidence demonstrates at least equivalent outcomes for the fibrin glue intervention [11]. Protocol amendments will be communicated to all relevant parties electronically.

To assure privacy and confidentiality, all data spreadsheets and consent forms will be kept in a locked cupboard throughout the trial, then transferred to a locked safe at the conclusion of the trial, where they will be kept for 15 years. Electronic copies of any forms will be kept on encrypted hard drives and patients will be deidentified in all data collection.

Dissemination

Once adequate data collection has been attained, dissemination of findings will occur via conference presentations and scientific journals. The researchers will also aim to present their findings at clinical
meetings in the north Queensland area where there is a potential impact on surgical practice patterns.

Discussion

The purpose of this trial is the evaluation of a new surgical technology in an alternative patient population to past research in this area. North Queensland has the highest rate of skin cancer in the world with an aging population susceptible to chronic disease and poor healing. In a systematic review of the literature, only two studies (with a total number of 54) out of 15 randomised controlled trials (with a cumulative number of 594) included patients with skin cancer at all[11]. This is clearly an area where further work is required, and it is particularly relevant to the population in regional North Queensland. In epidemiologic research tracking back several decades, Queensland, and in particular North Queensland where Townsville is situated, has been noted as the region with the highest incidence of skin cancer in the world [34-37]. The most recent of these studies notes a strong predilection towards elderly males and echoes the finding that these high rates of skin cancer likely relate to phenotypic predisposition (low Fitzpatrick skin type) and environmental exposures (UV radiation) [37]. Age predisposes to increased vascular disease or diabetes which impairs wound healing [38, 39]. As well as increased incidence of skin cancer, wound healing may be affected by the tropical climate in Townsville where mean maximum daily temperature ranges from 25.2 to 31.6 degrees Celsius and mean relative humidity between 50-70% throughout the year [40]. These weather patterns have been theorised to increase risk of infection due to humidity causing damp dressings which are an ideal environment for bacterial ingress and the authors’ clinical experience supports this [41]. This is a unique population in a unique setting of a humid tropical climate which likely contributes to higher infection rates and graft failure.

Therefore, this is a phase four clinical trial with a focus on pragmatic outcomes and to achieve this has a simple design. A pragmatic trial design is most appropriate to evaluate the broad applicability of this intervention across many populations. Controlling all patient factors would also limit the ability of this trial to answer the question of whether fibrin glue is superior in patients who do not have optimal wound healing. There are a few potential issues with the trial design, a major one being blinding of the surgeons utilising the fibrin glue. This is an issue evident in the use of any new surgical technology, as is the blinding of patients once they can see their wound during dressing changes. Therefore, we have implemented the use of blinded outcome assessors via photographs taken after removal of suture or staple affixation. There is also a possibility of a difference between the two comparators: staples and sutures. However, recent literature suggests equivalence between sutures and staples for all outcome measures except for post operative pain, where we plan to analyse sutures and staples separately.[42] We expect that this trial, like many, may have issues in recruitment however the patient pool is quite large and hopefully reasonable endpoints can be made. The use of sealed opaque envelopes and a specific order for allocation will also help reduce bias in allocation.

One issue which has been noted in other trials is the heterogeneity of chosen endpoints. Selection of specific endpoints for reporting in the literature is a potential issue, as is usage of different methods to measure endpoints. This may reflect differences in opinions as to which outcomes are important to measure but makes cross study comparisons difficult. For this study we have chosen several outcomes which reflect clinical measurements, patient reported measures and hospital system measures. We hope that this adequately captures the many levels of decision making involved in choosing to use new surgical technology.
Acknowledgements

The authors thank Ronny Gunnarsson for his guidance in trial design.

Competing Interests

None declared.

Funding

This work was supported by Townsville University Hospital SERTA Grant number 2018_14. Members of the grant committee did not have any role in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

Ethics Approval

This project has been reviewed and approved by the Townsville University Hospital Human Research Ethics Committee. HREC Reference number: HREC/17/QTHS/196

Author Contributions

EP conceived of the study idea and developed the protocol and study design. VV CH and MZ contributed to the development of the study design and protocol with VV also assisting with sample size calculation and statistics. All Authors contributed to the drafting of the manuscript.

References

1. Bergel, S., *Ueber Wirkungen des Fibrins*. Dtsch Med Wochenschr, 1909. 35(15): p. 663-665.
2. Spotnitz, W.D., *Fibrin Sealant: Past, Present, and Future: A Brief Review*. World Journal of Surgery, 2010. 34(4): p. 632-634.
3. Currie, L., J. Sharpe, and R. Martin, *The Use of Fibrin Glue in Skin grafts and Tissue-Engineered Skin Replacements: A Review*. Plastic and Reconstructive Surgery, 2001. 108(6): p. 1713-1726.
4. Brennan, M., *Fibrin Glue*. Blood Reviews, 1991. 5: p. 240-244.
5. Rousou, J., R. Engelman, and R. Breyer, *Fibrin Glue: An Effective Hemostatic Agent for Nonsuturable Intraoperative Bleeding*. The Annals of Thoracic Surgery, 1984. 38(4): p. 409-410.
6. Kjaergard, H.K. and U.S. Weis-Fogh, *Important factors influencing the strength of autologous fibrin glue; the fibrin concentration and reaction time--comparison of strength with commercial fibrin glue*. Eur Surg Res, 1994. 26(5): p. 273-6.
7. Buckley, R., et al., *A Simple Preparation of Autologous Fibrin Glue for Skin-Graft Fixation*. Plastic and Reconstructive Surgery, 1999. 103(1): p. 202-206.
8. Boeckx, W., et al., *Fibrin glue in the treatment of dorsal hand burns*. Burns, 1992. 18(5): p. 395-400.
9. McGill, V., et al. *Use of fibrin sealant in thermal injury*. Journal of burn care & rehabilitation, 1997. 18, 429-434.
10. Foster, K., et al., *Efficacy and safety of a fibrin sealant for adherence of autologous skin grafts to burn wounds: Results of a phase 3 clinical study*. Journal of Burn Care and Research, 2008. 29(2): p. 293-303.
11. Paw, E., et al., Effectiveness of fibrin glue in skin graft survival: A systematic review and meta-analysis. Annals of medicine and surgery (2012), 2020. 56: p. 48-55.
12. Maeda, M., et al., The role of serum imbibition for skin grafts. Plastic and reconstructive surgery, 1999. 104(7): p. 2100-2107.
13. Wilkinson, D., D. Askew, and A. Dixon, Skin cancer clinics in Australia: workload profile and performance indicators from an analysis of billing data. Medical Journal of Australia, 2006. 184(4): p. 162.
14. Sladden, M.J., et al., Surgical excision margins for primary cutaneous melanoma. Cochrane Database of Systematic Reviews, 2009(4).
15. Bishop, J.N., et al., The prevention, diagnosis, referral and management of melanoma of the skin: concise guidelines. Clinical medicine (London, England), 2007. 7(3): p. 283-290.
16. Shetty, S., M. Shetty, and A. Colaco, Can Use of fibrin glue in Peridontal Flap Surgery be an alternative to suturing? - A Review. International Journal of Advanced Research, 2015. 3(9): p. 1573-1575.
17. Lilius, P., Fibrin Adhesive: Its Use in Selected Skin Grafting. Scandinavian Journal of Plastic and Reconstructive Surgery, 2009. 21(3): p. 245-248.
18. Vedung, S. and A. Hedlund, Fibrin Glue: Its Use for Skin Grafting of Contaminated Burn Wounds in Areas Difficult to Immobilize. Journal of Burn Care & Rehabilitation, 1993. 14(3): p. 356-358.
19. Jabs, A.D., et al., The Effect of Fibrin Glue on Skin Grafts in Infected Sites. Plastic and Reconstructive Surgery, 1992. 89(2): p. 268-271.
20. Dvorak, H.F., et al., Fibrin Containing Gels Induce Angiogenesis. Laboratory Investigation, 1987. 57(6): p. 673-686.
21. Australian Bureau of Statistics. 2016 Census of Population and Housing. Australian Census 2016 [cited 2021 July 19]; Available from: https://quickstats.censusdata.abs.gov.au/census_services/getproduct/census/2016/quickstat/036.
22. Gorges, H., L. Hall, and C. Heal, Feasibility Study for a Randomised Controlled Trial for the Topical Treatment of Impetigo in Australian General Practice. Tropical Medicine and Infectious Disease, 2021. 6: p. 197.
23. Heal, C., et al., Building a bridge from the swamp to the ivory tower: Conducting randomised controlled trials in general practice. Aust J Gen Pract, 2018. 47(3): p. 153-157.
24. Ediriweera, Y., et al., A study protocol for a randomised controlled trial of ice to reduce the pain of immunisation: The ICE trial. Australian Journal of General Practice, 2022. 51: p. 173-177.
25. Chan, A.W., et al., SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. Bmj, 2013. 346: p. e7586.
26. Foster, K., et al., Efficacy and safety of a fibrin sealant for adherence of autologous skin grafts to burn wounds: results of a phase 3 clinical study. J Burn Care Res, 2008. 29(2): p. 293-303.
27. Hierner, R., et al., Skin grafting and wound healing—the “dermato-plastic team approach”. Clinics in Dermatology, 2005. 23(4): p. 343-352.
28. Jankowski, R., et al., [Hypersensitivity accidents to thrombin following the use of biological glues]. Ann Otolaryngol Chir Cervicofac, 1992. 109(2): p. 95-9.
29. Felema, G.G., et al., *Venous air embolism from Tisseel use during endoscopic cranial vault remodeling for craniosynostosis repair: a case report.* Paediatr Anaesth, 2013. **23**(8): p. 754-6.

30. Matsuse, S., A. Maruyama, and Y. Hara, *Nitrogenous subcutaneous emphysema caused by spray application of fibrin glue during retroperitoneal laparoscopic surgery.* Journal of Anaesthesia, 2011. **25**(3): p. 426.

31. Ohta, M., et al., *Complication caused by use of fibrin glue in vessel transposition for trigeminal neuralgia.* Neurol Med Chir (Tokyo), 2008. **48**(1): p. 30-2.

32. Faul, F., et al., *G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behavior Research Methods, 2007. **39**: p. 175-191.

33. StataCorp, *Stata Statistical Software: Release 16.* 2019, StataCorp LP: College Station, TX.

34. Stenbeck, K.D., et al., *Patterns of treated non-melanoma skin cancer in Queensland — the region with the highest incidence rates in the world.* Medical Journal of Australia, 1990. **153**(9): p. 511-515.

35. Silverstone, H. and J.H.A. Searle, *The Epidemiology of Skin Cancer in Queensland: The Influence of Phenotype and Environment.* British Journal of Cancer, 1970. **24**(2): p. 235-252.

36. Diepgen, T.L. and V. Mahler, *The epidemiology of skin cancer.* British Journal of Dermatology, 2002. **146**(s61): p. 1-6.

37. Raasch, B.A. and P.G. Buettner, *Multiple nonmelanoma skin cancer in an exposed Australian population.* International Journal of Dermatology, 2002. **41**(10): p. 652-658.

38. Thomas, D.R., *Age-Related Changes in Wound Healing.* Drugs & Aging, 2001. **18**(8): p. 607-620.

39. Vos, T., et al., *Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013.* The Lancet, 2015. **386**(9995): p. 743-800.

40. Commonwealth of Australia Bureau of Meteorology. *Climate statistics for Australian locations Townsville.* Climate statistics for Australian locations 2022 [cited 2022 26 April]; Available from: [http://www.bom.gov.au/climate/averages/tables/cw_032040_All.shtml](http://www.bom.gov.au/climate/averages/tables/cw_032040_All.shtml).

41. Heal, C., et al., *Can sutures get wet? Prospective randomised controlled trial of wound management in general practice.* BMJ, 2006. **332**(7549): p. 1053.

42. Cochetti, G., et al., *Surgical wound closure by staples or sutures?: Systematic review.* Medicine (Baltimore), 2020. **99**(25): p. e20573.
Figure Legend

Figure 1: A graphic to demonstrate the differences in skin graft fixation between sutures and staples (left) and fibrin glue (right).

Appendix 1 Example Participant Information and Consent Form

Table 1: WHO Trial Registration Data Set

| Primary registry and trial identifying number | Australian New Zealand Clinical Trials Registry ACTRN12618000484246 |
| Date of registration in primary registry | 04 April 2018 |
| Secondary identifying numbers | Nil |
| Source(s) of monetary or material support | Townsville University Hospital Grant |
| Primary sponsor | Townsville University Hospital Grant |
| Secondary sponsor(s) | Nil |
| Contact for public queries | EP, MBBS, MPH (ekta.paw@my.jcu.edu.au) |
| Contact for scientific queries | EP, MBBS, MPH (ekta.paw@my.jcu.edu.au) |
| Public title | Determining the Efficacy of Fibrin Glue in Skin grafts for Skin cancer (FiGSS): Open randomised clinical trial |
| Scientific title | Determining the Efficacy of Fibrin Glue in Skin grafts for Skin cancer (FiGSS): Open randomised clinical trial |
| Countries of recruitment | Australia |
| Health condition(s) or problem(s) studied | Skin cancer, Skin Graft Failure |
| Intervention(s) | Active comparator: Topical Fibrin Glue |
| | Placebo comparator: Suture or Staple Fixation |
| Ages eligible for study: ≥18 years |
| Sexes eligible for study: both |
| Accepts healthy volunteers: no |
| Key inclusion and exclusion criteria | Inclusion criteria: |
| | a) Will be undergoing surgery at one of the trial centres |
| | b) Have any histological type of skin cancer |
| | Exclusion criteria: a) Adverse reaction to the product (Fibrin Glue) |
| | b) Hypersensitivity to bovine protein |
| | c) Skin grafts on digits or genitalia |
| | d) Pregnancy |
| | e) Not cognitively intact to consent to participation |
| | f) Known immunodeficiency (HIV, Leukemia, etc), or haemolytic anaemia |
| | g) Skin conditions or medications affecting skin thickness and quality (e.g. prolonged corticosteroid use, autoimmune |

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| Study type        | Interventional |
|------------------|----------------|
| Allocation       | Randomized intervention model. Masking: open with blinded outcome assessors |
| Primary purpose  | Treatment |
| Phase            | IV |
| Date of first enrolment | April 2018 |
| Target sample size | 334 |
| Recruitment status | Recruiting |
| Primary outcome(s) | Graft take based on wound healing at one month |
| Key secondary outcomes | Pain on dressing changes and operative time. |
Patient/participant information sheet and consent form

Protocol name: Fibrin Glue in Skin Grafts for Skin Cancer (FiGSS)
Investigators: Principal investigator Ekta Paw BSc MBBS

1  Introduction

You are invited to take part in this research project. This is because you have a skin cancer which requires a skin graft. The research project is to compare different ways to attach skin grafts

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don’t understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don’t wish to take part, you don’t have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

• Understand what you have read
• Consent to take part in the research project
• Consent to have the tests and treatments that are described
• Consent to the use of your personal and health information as described.

2  What is the purpose of this research?

Skin cancer is incredibly common in North Queensland. Many people need large sections of skin removed to treat their cancer, and skin grafts to close their wounds. Instead of attaching these grafts with stitches or staples, a newer method is to use Fibrin glue, which is made from a protein found in humans which stops bleeding. By sticking to the whole surface of the graft, it is thought that Fibrin glue may improve healing. It may have an important effect in patients who are more likely to have graft failure, such as those with poor circulation, smokers, or the elderly.

Fibrin glue has been approved by the Australian Federal Government for use in attaching skin grafts for a number of years. There is research already on using it for burns, but not in skin cancer.
The results of this research will be used by the study doctor Ekta Paw to obtain a Masters of Philosophy degree.

3 What does participation in this research involve?

Participation in this project does not change your surgery. For some patients not participating in the trial we may also use the glue, as it is already part of usual care.

If there are no reasons you cannot participate in the study, you will be randomised to either: staples and stitches to attach your graft; or to the group which has fibrin glue to attach the graft. Your surgery will proceed as normal and your follow up appointments will be the same as normal (one week and one month). The only difference is that we will ask some questions about your medical history; your post-operative pain; and we will take photographs of your graft. The photographs will not include anything identifiable, and will only be seen by researchers to assess how well your wound has healed.

This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids study doctors or participants jumping to conclusions. Safety of the research will be monitored by a data safety management committee. There is also a study steering committee who will continually monitor progress and any unexpected events as they occur.

There are no additional costs associated with participating in this research project, nor will you be paid.

4 What do I have to do?

You will have to attend your surgery date as per usual, and your follow up appointments which are the same as if you were not participating in the study. It is important you attend these appointments on time as it will help assess the effectiveness of the glue. You can continue all your regular medications.

5 Other relevant information about the research project

There will be 334 patients participating in this study, of which half will have the glue used, and half will have stitches or staples used. There are two hospitals in Townsville involved.

6 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage. If you do decide
to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

**7 What are the alternatives to participation?**

If you don’t participate, your surgery will occur as usual, with the usual follow up. It is possible you may still have Fibrin glue used for your skin graft as it is part of the current standard of care.

**8 What are the possible benefits of taking part?**

We cannot guarantee or promise that you will receive any benefits from this research; however, possible benefits may include better healing of skin graft, less risk of infection, faster surgery and less pain after surgery. By taking part you may have an increase in the observation of your wounds and because of this problems or issues may be picked up faster. Taking part will enable doctors to know if this glue is truly better or not. If the glue is shown to improve outcomes, future patients may have better healing, less pain, less infections and need to attend hospital less often after having skin grafts.

**9 What are the possible risks and disadvantages of taking part?**

While Fibrin glue has been approved by the Australian Federal Government, there have been a small number of adverse outcomes reported which have been associated with its use. These have mainly related to hypersensitivity reactions to the proteins. It is for this reason that we will not allow people who have a known allergy to bovine protein to participate in this study. However, it is possible you may have an allergy without knowing about it previously. Allergy reactions can range from itchiness and redness, to difficulty breathing and a drop in blood pressure. While this is a very rare occurrence, if it does occur it will be within a very short time of exposure to the allergen (Fibrin glue), and you will be closely monitored during and after your surgery for any signs of this so it can be treated quickly.

**10 What if I withdraw from this research project?**

You are welcome to withdraw from this research project at any time if you no longer wish to be a participant. Your surgery and follow up will go ahead as usual, with no change to the timing or quality of your care. Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with Townsville Hospital/Mater Health Services North Queensland.

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the
research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the sponsor up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

11 Could this research project be stopped unexpectedly?
This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as:

• Unacceptable side effects
• The treatment being shown not to be effective
• The treatment being shown to work and not need further testing

12 What will happen to information about me?
By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project will be that can identify you will remain confidential. Data will be kept in a form which does not identify you, but in case we need to re-identify a participant for medical reasons there will be a code. This code will be kept securely in a password protected electronic format which can only be accessed by the researchers involved in this study. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law. Data will be kept securely for 15 years following completion of the study as per James Cook University guidelines.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form you agree to the study team accessing health records if they are relevant to your participation in this research project.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission. Data will only be presented as numerical results with no identification of individual participants.
13 Complaints and compensation

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

14 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of Townsville Hospital.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research* (2007). This statement has been developed to protect the interests of people who agree to participate in human research studies.

15 Further information and who to contact

The person you may need to contact will depend on the nature of your query. If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor on 4433 1111 or any of the following people: Dr Mark Zonta, Dr Venkat Vangaveti.

Research Contact Person:
Name: Dr Ekta Paw
Position: Principal House Officer, General Surgery
Phone: 4433 1111
Email: ekta.paw@health.qld.gov.au

This project has been reviewed and approved by the Townsville Hospital and Health Service Human Research Ethics Committee. For concerns relating the conduct of this project contact:
HREC Chairperson
Phone: 07 4433 1440
Email: TSV-Ethics-Committee@health.qld.gov.au
PATIENT/PARTICIPANT CONSENT FORM

PROTOCOL NAME: Fibrin Glue in Skin Grafts for Skin Cancer (FiGSS)

INVESTIGATORS: Principal investigator Ekta Paw BSc MBBS

1. The nature and purpose of the research project has been explained to me. I understand it and acknowledge that taking part in this study is voluntary.

2. I have been given an Information Sheet which explains the purpose of the study, the possible benefits, and the possible risks.

3. I understand that I may not directly benefit from taking part in the trial.

4. I understand that, while information gained during the study may be published, I will not be identified and my personal results will remain confidential.

5. I understand that I can withdraw from the study at any stage and that it will not affect my medical care, now or in the future.

6. I have had the opportunity to discuss taking part in this investigation with a family member or friend.

NAME OF PARTICIPANT: __________________________

SIGNATURE: __________________________

DATED: __________________________

I certify that I have explained the study to the patient/volunteer and consider that he/she understands what is involved.

NAME OF PRINCIPAL INVESTIGATOR: Dr Ekta Paw

SIGNATURE: __________________________

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

**Instructions to authors**

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

| Reporting Item | Page Number |
|----------------|-------------|
| Administrative information | |
| Title | #1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym |
| Trial registration | #2a | Trial identifier and registry name. If not yet registered, name of intended registry |
| Trial registration: data set | #2b | All items from the World Health Organization Trial Registration Data Set |
| Protocol version | #3 | Date and version identifier |
| Funding | #4 | Sources and types of financial, material, and other support |
| Roles and responsibilities: contributorship | #5a | Names, affiliations, and roles of protocol contributors |
Roles and responsibilities: sponsor contact information

Roles and responsibilities: sponsor and funder

Roles and responsibilities: committees

Introduction

Background and rationale

Background and rationale: choice of comparators

Objectives

Trial design

Methods:
Participants, interventions, and outcomes

Study setting

Eligibility criteria
perform the interventions (eg, surgeons, psychotherapists)

Interventions: #11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered

Interventions: #11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)

Interventions: #11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)

Interventions: #11d Relevant concomitant care and interventions that are permitted or prohibited during the trial

Outcomes #12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended

Participant timeline #13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)

Sample size #14 Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations

Recruitment #15 Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation: sequence generation #16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
| Method                                      | Description                                                                                                                                                                                                 |
|--------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Allocation concealment mechanism           | Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned |
| Allocation: implementation                | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions                                                                                       |
| Blinding (masking)                         | Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how                                                              |
| Blinding (masking): emergency unblinding   | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial                                                         |

**Methods: Data collection, management, and analysis**

| Data collection plan                        | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol |
|--------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Data collection plan: retention            | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols |
| Data management                            | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol |
| Statistics: outcomes                      | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol |
| Statistics: additional analyses            | Methods for any additional analyses (e.g., subgroup and adjusted analyses) |
Statistics: analysis population and missing data

#20c Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

Methods: Monitoring

Data monitoring: formal committee

#21a Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

Data monitoring: interim analysis

#21b Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial

Harms

#22 Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct

Auditing

#23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval

#24 Plans for seeking research ethics committee / institutional review board (REC / IRB) approval

Protocol amendments

#25 Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)

Consent or assent

#26a Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)

Consent or assent: ancillary studies

#26b Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

Confidentiality

#27 How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests #28 Financial and other competing interests for principal investigators for the overall trial and each study site

Data access #29 Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators

Ancillary and post trial care #30 Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation

Dissemination policy: trial results #31a Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions

Dissemination policy: authorship #31b Authorship eligibility guidelines and any intended use of professional writers

Dissemination policy: reproducible research #31c Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials #32 Model consent form and other related documentation given to participants and authorised surrogates

Biological specimens #33 Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

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Protocol for an open randomised controlled trial investigating Fibrin Glue in Skin grafts for Skin cancer (FiGSS)

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Protocol for an open randomised controlled trial investigating Fibrin Glue in Skin grafts for Skin cancer (FiGSS)

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Abstract

Introduction

Skin cancer is a common disease in the tropics, and oncologic resection typically requires reconstruction with skin grafts. Fibrin glue, initially established as a haemostatic agent, has been studied extensively as an adhesive for skin grafts in burns. This study aims to investigate the use of fibrin as an adhesive for split skin grafts in skin cancers.

Methods and Analysis

The study design is a prospective randomised controlled trial with the aim of investigating the impact of two different methods of split skin graft fixation. The intervention of fibrin glue will be compared to the control of staples or sutures. The trial will be conducted at two sites, a public and private hospital in Townsville, Australia over a 24 month period with 334 participants to be recruited. Consecutive patients presenting for skin excisions and grafting will be eligible to participate. Randomisation will be on the level of the patient. The primary outcome is graft take based on wound healing at one month. Secondary outcomes will be pain on dressing changes and operative time.

Ethics and Dissemination

The study has been approved by The Townsville University Hospital Human Research Ethics Committee (HREC). Findings will be disseminated in conference presentations and journals and through online electronic media.

Registration Details

Registered on Australian New Zealand Clinical Trials Registry ACTRN12618000484246

Strengths and Limitations

Study Strengths

- Practical question, clinically relevant to surgical management of skin cancer
- Blinded independent outcome assessor will assess photographs of all wounds
- Outcomes include clinical measurements, patient reported measures and hospital system measures

Study Limitations

- Surgeons and patients cannot be blinded
- Assessment of graft take has an element of subjectivity

Introduction

The first described use of intraoperative Fibrin was in 1909 when German surgeons used it as a haemostatic agent [1, 2]. When Fibrin is introduced to a wound alongside Thrombin, Factor XIII and Calcium it mimics the final events in the clotting cascade, cleaving Fibrinogen to Fibrin [3-5]. Fibrin was originally derived from patient plasma intraoperatively, but now commercial preparations of Fibrin glue are now available with high concentrations of Fibrin which can be used as an adhesive.
Fibrin glue has been investigated for adhesive use in skin grafts for burns and shown no inferiority to peripheral fixation (staples/sutures) in terms of wound closure [8-11]. Specifically, Fibrin glue adheres the entire graft surface to the wound bed (figure 1) and significantly reduces the formation of haematoma or seroma immediately post operatively [10]. Studies have also shown use of Fibrin glue results in decreased dressing requirements to ensure close adherence of the graft; better haemostasis; and less contraction of scar tissue [8-10]. Skin graft survival is dependent on vascularisation of the graft which usually begins after two or three days. During this initial period poor adherence or hematoma or seroma formation can reduce graft imbibition of oxygen and nutrients from the graft bed and disrupt further vascularisation [10, 12]. Formation of a hematoma or seroma is the most common cause for graft failure [10, 12]. Issues with the graft recipient site such as poor vascularity, infection, inflammation, or shearing forces over mobile skin areas can also lead to graft failure [10]. After wound closure, the graft site can also contract, leading to aesthetic defects or functional defects due to reduced range of motion [6].

In Australia, and particularly Far North Queensland, skin cancers are incredibly common and many patients have skin cancers which are sizeable enough to require grafting after resection for adequate wound closure [13]. This is particularly true of melanoma patients where the surgical margins range from one centimetre upwards [14]. This margin results in an area of skin loss usually at least three centimetres across which cannot be primarily closed, particularly in extremities due to taught skin. Many of these patients are elderly and may have diseases which impair wound healing. One of the most common sites for skin cancer is the lower leg, which is particularly prone to poor healing in the presence of vascular risk factors [15] Previous studies have not addressed the use of Fibrin glue in skin cancer resections nor in elderly patients and patients with vascular risk factors. Fibrin glue has been investigated for use in other difficult to graft situations such as infected sites, mobile skin areas and difficult to graft areas with good results [8, 16-19]. These are all areas which can contribute to skin graft failure. It is possible that Fibrin glue can increase graft take in patients who have vascular issues as it has been shown that increased Fibrin decreases likelihood of graft failure and can induce angiogenesis [20]. If Fibrin glue can be shown to be beneficial in skin cancer patients (particularly elderly and vasculopathic patients) and significantly decrease operative time and follow up it may be a viable alternative to sutures. This could potentially change the management of skin grafts to become quicker, easier and less painful for patients with less follow up required.

There have been no clinical trials looking at the use of Fibrin glue for skin grafts in skin cancer to date. [11] There have been few trials of reasonable size looking at the use of Fibrin glue in skin grafts for burns. [10, 11] These trials have shown apparent benefits in using Fibrin glue, and it may be an effective way to improve graft take. Currently the accepted standard of care would be use of any of these techniques, however, the use of glue is less common.

The objective of this study is to examine the effectiveness of Fibrin glue in reconstruction of oncologic skin resection. If our research demonstrates increased effectiveness of glue it may lead to a change in behaviour which may reduce the incidence of graft failure in this patient population.

Methods and Analysis

Study Centre

This study will be conducted in Townsville, Queensland (Latitude 19.2590° S). Townsville is a regional centre with a population of approximately 200,000 [21] with only two hospitals. One hospital is government funded with the other privately funded, and patients will be recruited from both sites.
Members of the study team have conducted multiple randomised controlled trials (RCTs) on skin excisions in the North Queensland region. [22-24]

Study Design

This is a prospective randomized controlled clinical trial (RCT). The intervention group will have grafts secured with Fibrin glue applied across the entire graft bed (figure 1). The normal treatment control group will have grafts secured peripherally only with sutures or staples. These methods apply in both public and private hospital settings. Data will be collected over a 24 month period. The study will be reported in accordance with the CONSORT statement. Clinical Trial Protocol version 5 dated 22/10/19 and WHO Trial Registration Data Set provided in Table 1. We used the SPIRIT checklist when writing our report [25].

Intervention

The Fibrin glue being used in this study is already in clinical use under the brand name ARTISS. It consists of two syringes, each containing human plasma derived coagulation factors which when mixed, initiate coagulation and form a clot. It has had Australian Therapeutic Goods Administration approval since 2010. This study specifically examines the effect of intraoperative application of a thin layer of Fibrin glue across the entire graft bed immediately prior to the skin graft placement. This is diagrammatically represented in Figure 1.

Recruitment of Study Participants

Patients will be recruited in the process of booking for surgery. Potential patients will be identified in two places: at surgical clinics and during the booking process for surgery. Clinicians will discuss study participation with patients who are undergoing skin grafts for skin cancer. If the patient declines, then no further action is required. If the patient accepts, clinicians will check that they fit the inclusion criteria and provide an information sheet and consent form (Appendix 1). Informed consent will be discussed by the recruiting clinician.

Randomization

Randomisation will be performed at the level of the patient with an allocation ratio of 1:1. A computer generated random number table will create random numbers in blocks of 2 or 4 and block size will be randomised. The patient allocation will be provided in sequential, opaque, sealed, tamperproof envelopes. Patients and clinicians will only be aware of the treatment allocation after the patient has been recruited into the trial. Blinding of the patient and the treating clinician to the intervention will not be possible, however, an independent outcome assessor will be blinded to treatment allocation.

Inclusion Criteria

All patients presenting to surgical clinics requiring skin grafting will be potential participants. They will be assessed to see if they meet the following inclusion criteria:

a) Will be undergoing surgery at one of the trial centres
b) Have any histological type of skin cancer
c) Age ≥ 18 years

Exclusion Criteria

The exclusion criteria for this study are:
a) Adverse reaction to the product  
b) Hypersensitivity to bovine protein  
c) Skin grafts on digits or genitalia  
d) Pregnancy  
e) Not cognitively intact to consent to participation  
f) Known immunodeficiency (HIV, Leukemia, etc), or haemolytic anaemia  
g) Skin conditions or medications affecting skin thickness and quality (e.g. prolonged corticosteroid use, autoimmune conditions of skin)  
h) Chronic malnourishment

Surgical and Wound Protocol

The surgical and wound management protocol is to standardise management across the study arms. This is modelled on similar protocols and in consultation with participating clinicians.[26, 27] Intraoperative application of Fibrin glue includes standardised technique and timing. Dressings have been standardised at all wound sites to include a paraffin-based gauze dressing directly on the wound site, followed by foam dressing and an adhesive, non-woven fabric. Patients received standard postoperative and wound care instructions, and all had two follow up appointments at the specialist clinic at one week and one month.

Outcome Measures

The primary outcome of graft take will be measured based on review at one month post operatively, including photographic data and clinical reports of wound healing and graft take. Graft healing at one week will also be examined as a secondary outcome measure. Additional secondary outcomes will include reported pain post dressing change scores and operative time. Subgroup analysis of patients who have vascular risk factors (including smoking, hypertension, diabetes, hypercholesterolaemia) or vascular disease (myocardial infarction, stroke, or other vascular disease) will be performed.

Outcome assessors at the time of clinical assessment include surgical medical practitioners or nursing staff with specific wound management skills. Although outcome assessors are not advised of allocations, due to the nature of sutures or staples being present in the wound at some points of assessment, allocation may be evident to the initial outcome assessors. To mitigate this bias, independent blinded outcome assessors will be shown photographs to estimate graft take. Both assessments will be compared in the analysis.

Secondary outcome measures include pain on dressing changes, operative time, and adverse events.

Definitions

Graft take is defined as wound healing over grafted areas within the period of weeks after the skin graft procedure, rather than healing via secondary intention and granulation tissue in a prolonged period. This will be assessed both clinically and photographically to reduce inter observer variability.

Pain on dressing change is a patient reported outcome where patients will indicate pain on a ten point scale with the assistance of the Wong-Baker pain faces chart. Operative time is defined as the time from first incision of the lesion until final dressing placement over the wound.

Data Collection

Patient characteristics:
When patients are recruited to the study, they will fill out a simple questionnaire with their gender, age, and a targeted medical history.

Operative Data:

Operative time will be recorded for all procedures, as well as graft site and size.

Post-operative Data:

At one week follow up, blinded assessors will assess graft take or rejection and photos will be taken for independent validation. Patients will be asked to rate their post procedure and dressing change pain on a pain scale.

At one month follow up, blinded assessors will assess graft take or rejection and photos will be taken for independent validation.

Surgical site infections and incidence of post-operative haematoma and seroma will be noted at any time post operatively, as will any other relevant outcomes or management (e.g. unexpected prolonged inpatient stay or use of hydrocortisone or silver nitrate to manage hypergranulation).

An adverse event would be an outcome not expected in the usual peri-operative or post-operative course of the patient which is related to the use of Fibrin glue. The analysis from the Therapeutic Goods Administration in 2010 determined that none of the adverse effects noted in the trial were due to the Fibrin glue and there were no significant safety issues. A literature search of Medline and Embase looking for papers with the terms ‘tissue adhesive’ and related terms with ‘adverse effect’ and related terms found a total 589 papers. Out of all these papers, only four cases of hypersensitivity were noted, with two cases of anaphylaxis [28]. Three cases noted adverse events resulting from incorrect application of glue (air embolus, subcutaneous emphysema, and incidental adhesion to surrounding structures) [29-31]. Patients with a hypersensitivity to bovine protein will be excluded from the trial as a precaution. Additionally, all surgeons administering the glue have experience and knowledge in the proper application. If any adverse events were to occur, then they would be discussed with the chair of the steering committee who would determine if an extra meeting of the committee would be required and notify the data safety monitoring committee and the human research and ethics committee. A logbook of adverse effects would also be kept, including those which are not related to Fibrin glue.

For data safety management, patient data will be collected in a de-identified format, with a potential for re-identification for situations of adverse events. The re-identification code will be password protected, as will the data collected and will only be able to be accessed by the principal investigator and co-investigators.

Due to the size of the trial a trial management group consisting of both clinicians and researchers was established. One independent person was deemed to be sufficient as an independent data-monitor who has no affiliation with the management group. The positive stopping rule for the trial management group for each interim analysis is 25% recruited (p<0.0000001); 50% recruited (p<0.000001); 75% recruited (p<0.00001). If patients with Fibrin glue show a worse rate of graft take, the negative stopping rule is p<0.05.

Sample Size Calculation

A two tailed analysis assuming a power of 0.80 and alpha of 0.05 gave 334 patients in total with 167 in each group [32]. It would likely take approximately one to two years to recruit enough patients for this study. Sample size was determined by power testing with similar papers, one of which
compared approximately 300 cases of split skin graft [26]. In this paper at day 28 approximately 68% of participants had 100% take of skin graft in the group using sutures or staples rather than Fibrin glue and a 10% difference was considered significant. An estimate of graft take in the general population patients would be drawn from was roughly estimated as 50% and a clinically significant difference was determined to be 15% for this study.

**Data Analysis**

Graft take will be compared based on review at one week and one month post operatively, including photographic data and reported wound healing and graft take. Groups will be compared using a two proportion z-test. A subgroup analysis on the impact of vascular risk factors will be performed, as well as on haematoma and seroma formation, although the study is not powered for this analysis.

Data will be analysed using statistical software StataSE 16 [33]. Demographic data will be presented as percentages. Continuous variables will be tested for normality and based on the outcome of the test, parametric or non-parametric analyses of the data will be undertaken. Z-test analysis to compare two proportions will be used for analysis of graft take. A p value of <0.05 will be considered statistically significant. The data may also be used in aggregate to conduct a cost effectiveness analysis.

**Potential Problems**

Based on the number of patients seen in both hospitals presently for skin cancer excisions, we believe that recruitment of adequate numbers is feasible. However, if we fail to recruit enough patients, other North Queensland hospital sites may be approached and invited to participate.

Patients currently attend for wound redressing appointments initially at the hospital where their operation is performed. After these initial reviews if further dressings are required and the patient has a significant travel time then community dressings may be organised. Given that most patients already receive their wound care within the hospital they will have their post operative outcomes assessed at these appointments.

**Patient and Public Involvement**

Patient and public representatives were present on the Ethics Committee reviewing the design and research. Results from this trial will be reported publicly.

**Ethics and Dissemination**

**Ethical Considerations**

We do not expect the intervention in this study to place participants at any significant risk of harm, as current evidence demonstrates at least equivalent outcomes for the Fibrin glue intervention [11]. Protocol amendments will be communicated to all relevant parties electronically.

To assure privacy and confidentiality, all data spreadsheets and consent forms will be kept in a locked cupboard throughout the trial, then transferred to a locked safe at the conclusion of the trial, where they will be kept for 15 years. Electronic copies of any forms will be kept on encrypted hard drives and patients will be deidentified in all data collection.

This project has been reviewed and approved by the Townsville University Hospital Human Research Ethics Committee. HREC Reference number: HREC/17/QTHS/196
Dissemination

Once adequate data collection has been attained, dissemination of findings will occur via conference presentations and scientific journals. The researchers will also aim to present their findings at clinical meetings in the North Queensland area where there is a potential impact on surgical practice patterns.

Discussion

The purpose of this trial is the evaluation of a new surgical technology in an alternative patient population to previous research in this area. North Queensland has the highest rate of skin cancer in the world and an aging population which is susceptible to chronic disease and poor healing. In a systematic review of the literature, only two studies (with a total number of 54) out of 15 randomised controlled trials (with a cumulative number of 594) included patients with skin cancer at all [11]. This is clearly an area where further work is required, and it is particularly relevant to the population in regional North Queensland. In epidemiologic research tracking back several decades, Queensland, and in particular North Queensland where Townsville is situated, has been noted as the region with the highest incidence of skin cancer in the world [34-37]. The most recent of these studies notes a strong predilection towards elderly males and echoes the finding that these high rates of skin cancer likely relate to phenotypic predisposition (low Fitzpatrick skin type) and environmental exposures (UV radiation) [37]. Age predisposes to increased vascular disease or diabetes which impairs wound healing [38, 39]. As well as increased incidence of skin cancer, wound healing may be affected by the tropical climate in Townsville where mean maximum daily temperature ranges from 25.2 to 31.6 degrees Celsius and mean relative humidity between 50-70% throughout the year [40]. These weather patterns have been theorised to increase risk of infection due to humidity causing damp dressings which are an ideal environment for bacterial ingress and the authors’ clinical experience supports this [41]. This is a unique population in a unique setting of a humid tropical climate which likely contributes to higher infection rates and graft failure.

Therefore, this is a phase four clinical trial with a focus on pragmatic outcomes and to achieve this has a simple design. A pragmatic trial design is most appropriate to evaluate the broad applicability of this intervention. Controlling all patient factors would also limit the ability of this trial to answer the question of whether Fibrin glue is superior in patients who do not have optimal wound healing. There are a few potential issues with the trial design, a major one being blinding of the surgeons utilising the Fibrin glue, which is an issue evident in the use of any new interoperative surgical technology. Similarly, there is an issue with the blinding of patients once they can see their wound during dressing changes. Therefore, we have implemented the use of blinded outcome assessors via photographs taken after removal of suture or staple affixation. There is also a possibility of a difference between the two comparators: staples and sutures. However, recent literature suggests equivalence between sutures and staples for all outcome measures except for post operative pain, where we plan to analyse sutures and staples separately.[42] We expect that this trial, like many, may have issues in recruitment but the patient pool is quite large and hopefully reasonable endpoints can be made. The use of sealed opaque envelopes and a specific order for allocation will also reduce allocation bias.

One issue which has been noted in other trials is the heterogeneity of chosen endpoints. Selection of specific endpoints for reporting in the literature is a potential issue, as is usage of different methods to measure endpoints. This may reflect differences in opinion as to which outcomes are important to measure but makes pooled data comparisons difficult. For this study we have chosen several outcomes which reflect several areas including clinical measures; patient reported measures; and
hospital system measures. We hope that this adequately captures the many levels of decision making involved in choosing to use new surgical technology.

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Competing Interests

None declared.

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Author Contributions

EP conceived of the study idea and developed the protocol and study design. VV CH and MZ contributed to the development of the study design and protocol with VV also assisting with sample size calculation and statistics. All Authors contributed to the drafting of the manuscript.

References

1. Bergel, S., Ueber Wirkungen des Fibrins. Dtsch Med Wochenschr, 1909. 35(15): p. 663-665.
2. Spotnitz, W.D., Fibrin Sealant: Past, Present, and Future: A Brief Review. World Journal of Surgery, 2010. 34(4): p. 632-634.
3. Currie, L., J. Sharpe, and R. Martin, The Use of Fibrin Glue in Skin Grafts and Tissue-Engineered Skin Replacements: A Review. Plastic and Reconstructive Surgery, 2001. 108(6): p. 1713-1726.
4. Brennan, M., Fibrin Glue. Blood Reviews, 1991. 5: p. 240-244.
5. Rousou, J., R. Engelman, and R. Breyer, Fibrin Glue: An Effective Hemostatic Agent for Nonsuturable Intraoperative Bleeding. The Annals of Thoracic Surgery, 1984. 38(4): p. 409-410.
6. Kjaergard, H.K. and U.S. Weis-Fogh, Important factors influencing the strength of autologous fibrin glue; the fibrin concentration and reaction time--comparison of strength with commercial fibrin glue. Eur Surg Res, 1994. 26(5): p. 273-6.
7. Buckley, R., et al., A Simple Preparation of Autologous Fibrin Glue for Skin-Graft Fixation. Plastic and Reconstructive Surgery, 1999. 103(1): p. 202-206.
8. Boeckx, W., et al., Fibrin glue in the treatment of dorsal hand burns. Burns, 1992. 18(5): p. 395-400.
9. McGill, V., et al. Use of fibrin sealant in thermal injury. Journal of burn care & rehabilitation, 1997. 18, 429-434.
10. Foster, K., et al., Efficacy and safety of a fibrin sealant for adherence of autologous skin grafts to burn wounds: Results of a phase 3 clinical study. Journal of Burn Care and Research, 2008. 29(2): p. 293-303.
11. Paw, E., et al., *Effectiveness of fibrin glue in skin graft survival: A systematic review and meta-analysis*. Annals of medicine and surgery (2012), 2020. 56: p. 48-55.

12. Maeda, M., et al., *The role of serum imbibition for skin grafts*. Plastic and reconstructive surgery, 1999. 104(7): p. 2100-2107.

13. Wilkinson, D., D. Askew, and A. Dixon, *Skin cancer clinics in Australia: workload profile and performance indicators from an analysis of billing data*. Medical Journal of Australia, 2006. 184(4): p. 162.

14. Sladden, M.J., et al., *Surgical excision margins for primary cutaneous melanoma*. Cochrane Database of Systematic Reviews, 2009(4).

15. Bishop, J.N., et al., *The prevention, diagnosis, referral and management of melanoma of the skin: concise guidelines*. Clinical medicine (London, England), 2007. 7(3): p. 283-290.

16. Shetty, S., M. Shetty, and A. Colaco, *Can Use of fibrin glue in Peridontal Flap Surgery be an alternative to suturing? - A Review*. International Journal of Advanced Research, 2015. 3(9): p. 1573-1575.

17. Lilius, P., *Fibrin Adhesive: Its Use in Selected Skin Grafting*. Scandinavian Journal of Plastic and Reconstructive Surgery, 2009. 21(3): p. 245-248.

18. Vedung, S. and A. Hedlund, *Fibrin Glue: Its Use for Skin Grafting of Contaminated Burn Wounds in Areas Difficult to Immobilize*. Journal of Burn Care & Rehabilitation, 1993. 14(3): p. 356-358.

19. Jabs, A.D., et al., *The Effect of Fibrin Glue on Skin Grafts in Infected Sites*. Plastic and Reconstructive Surgery, 1992. 89(2): p. 268-271.

20. Dvorak, H.F., et al., *Fibrin Containing Gels Induce Angiogenesis*. Laboratory Investigation, 1987. 57(6): p. 673-686.

21. Australian Bureau of Statistics. *2016 Census of Population and Housing*. Australian Census 2016 [cited 2021 July 19]; Available from: [https://quickstats.censusdata.abs.gov.au/census_services/getproduct/census/2016/quickstat/036](https://quickstats.censusdata.abs.gov.au/census_services/getproduct/census/2016/quickstat/036).

22. Gorges, H., L. Hall, and C. Heal, *Feasibility Study for a Randomised Controlled Trial for the Topical Treatment of Impetigo in Australian General Practice*. Tropical Medicine and Infectious Disease, 2021. 6: p. 197.

23. Heal, C., et al., *Building a bridge from the swamp to the ivory tower: Conducting randomised controlled trials in general practice*. Aust J Gen Pract, 2018. 47(3): p. 153-157.

24. Ediriweera, Y., et al., A study protocol for a randomised controlled trial of ice to reduce the pain of immunisation: The ICE trial. Australian Journal of General Practice, 2022. 51: p. 173-177.

25. Chan, A.W., et al., *SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials*. Bmj, 2013. 346: p. e7586.

26. Foster, K., et al., *Efficacy and safety of a fibrin sealant for adherence of autologous skin grafts to burn wounds: results of a phase 3 clinical study*. J Burn Care Res, 2008. 29(2): p. 293-303.

27. Hierner, R., et al., *Skin grafting and wound healing—the “dermato-plastic team approach”*. Clinics in Dermatology, 2005. 23(4): p. 343-352.

28. Jankowski, R., et al., [Hypersensitivity accidents to thrombin following the use of biological glues]. Ann Otolaryngol Chir Cervicofac, 1992. 109(2): p. 95-9.
29. Felema, G.G., et al., *Venous air embolism from Tisseel use during endoscopic cranial vault remodeling for craniosynostosis repair: a case report.* Paediatr Anaesth, 2013. 23(8): p. 754-6.

30. Matsuse, S., A. Maruyama, and Y. Hara, *Nitrogenous subcutaneous emphysema caused by spray application of fibrin glue during retroperitoneal laparoscopic surgery.* Journal of Anesthesia, 2011. 25(3): p. 426.

31. Ohta, M., et al., *Complication caused by use of fibrin glue in vessel transposition for trigeminal neuralgia.* Neurol Med Chir (Tokyo), 2008. 48(1): p. 30-2.

32. Faul, F., et al., *G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences.* Behavior Research Methods, 2007. 39: p. 175-191.

33. StataCorp, *Stata Statistical Software: Release 16.* 2019, StataCorp LP: College Station, TX.

34. Stenbeck, K.D., et al., *Patterns of treated non-melanoma skin cancer in Queensland — the region with the highest incidence rates in the world.* Medical Journal of Australia, 1990. 153(9): p. 511-515.

35. Silverstone, H. and J.H.A. Searle, *The Epidemiology of Skin Cancer in Queensland: The Influence of Phenotype and Environment.* British Journal of Cancer, 1970. 24(2): p. 235-252.

36. Diepgen, T.L. and V. Mahler, *The epidemiology of skin cancer.* British Journal of Dermatology, 2002. 146(s61): p. 1-6.

37. Raasch, B.A. and P.G. Buettner, *Multiple nonmelanoma skin cancer in an exposed Australian population.* International Journal of Dermatology, 2002. 41(10): p. 652-658.

38. Thomas, D.R., *Age-Related Changes in Wound Healing.* Drugs & Aging, 2001. 18(8): p. 607-620.

39. Vos, T., et al., *Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013.* The Lancet, 2015. 386(9995): p. 743-800.

40. Commonwealth of Australia Bureau of Meteorology. *Climate statistics for Australian locations Townsville.* Climate statistics for Australian locations 2022 [cited 2022 26 April]; Available from: [http://www.bom.gov.au/climate/averages/tables/cw_032040_All.shtml](http://www.bom.gov.au/climate/averages/tables/cw_032040_All.shtml).

41. Heal, C., et al., *Can sutures get wet? Prospective randomised controlled trial of wound management in general practice.* BMJ, 2006. 332(7549): p. 1053.

42. Cochetti, G., et al., *Surgical wound closure by staples or sutures?: Systematic review.* Medicine (Baltimore), 2020. 99(25): p. e20573.
**Figure Legend**

Figure 1: A graphic to demonstrate the differences in skin graft fixation between sutures and staples (left) and fibrin glue (right).

**Appendix 1 Example Participant Information and Consent Form**

**Table 1: WHO Trial Registration Data Set**

| Primary registry and trial identifying number | Australian New Zealand Clinical Trials Registry ACTRN12618000484246 |
|-----------------------------------------------|---------------------------------------------------------------------|
| Date of registration in primary registry      | 04 April 2018                                                      |
| Secondary identifying numbers                | Nil                                                                |
| Source(s) of monetary or material support    | Townsville University Hospital Grant                                |
| Primary sponsor                              | Townsville University Hospital Grant                                |
| Secondary sponsor(s)                         | Nil                                                                |
| Contact for public queries                   | EP, MBBS, MPH (ekta.paw@my.jcu.edu.au)                              |
| Contact for scientific queries               | EP, MBBS, MPH (ekta.paw@my.jcu.edu.au)                              |
| Public title                                 | Determining the Efficacy of Fibrin Glue in Skin grafts for Skin cancer (FiGSS): Open randomised clinical trial |
| Scientific title                             | Determining the Efficacy of Fibrin Glue in Skin grafts for Skin cancer (FiGSS): Open randomised clinical trial |
| Countries of recruitment                     | Australia                                                          |
| Health condition(s) or problem(s) studied    | Skin cancer, Skin Graft Failure                                     |
| Intervention(s)                              | Active comparator: Topical Fibrin Glue                              |
|                                               | Placebo comparator: Suture or Staple Fixation                      |
| Ages eligible for study: ≥18 years            |                                                                     |
| Sexes eligible for study: both               |                                                                     |
| Accepts healthy volunteers: no               |                                                                     |
| Inclusion criteria:                          |                                                                      |
| a) Will be undergoing surgery at one of the trial centres | |
| b) Have any histological type of skin cancer |                                                                      |
| Exclusion criteria:                          |                                                                      |
| a) Adverse reaction to the product (Fibrin Glue) |                                                                      |
| b) Hypersensitivity to bovine protein         |                                                                      |
| c) Skin grafts on digits or genitalia        |                                                                      |
| d) Pregnancy                                |                                                                      |
| e) Not cognitively intact to consent to participation | |
| f) Known immunodeficiency (HIV, Leukemia, etc), or haemolytic anaemia | |
| g) Skin conditions or medications affecting skin thickness and quality (e.g. prolonged corticosteroid use, autoimmune |
| Study type       | Interventional |
|------------------|----------------|
| Allocation       | Randomized intervention model. Masking: open with blinded outcome assessors |
| Primary purpose  | Treatment      |
| Phase            | IV             |
| Date of first enrolment | April 2018 |
| Target sample size | 334     |
| Recruitment status | Recruiting |
| Primary outcome(s) | Graft take based on wound healing at one month |
| Key secondary outcomes | Pain on dressing changes and operative time. |
Patient/participant information sheet and consent form

Protocol name: Fibrin Glue in Skin Grafts for Skin Cancer (FiGSS)
Investigators: Principal investigator Ekta Paw BSc MBBS

1 Introduction

You are invited to take part in this research project. This is because you have a skin cancer which requires a skin graft. The research project is to compare different ways to attach skin grafts

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don’t understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don’t wish to take part, you don’t have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

• Understand what you have read
• Consent to take part in the research project
• Consent to have the tests and treatments that are described
• Consent to the use of your personal and health information as described.

2 What is the purpose of this research?

Skin cancer is incredibly common in North Queensland. Many people need large sections of skin removed to treat their cancer, and skin grafts to close their wounds. Instead of attaching these grafts with stitches or staples, a newer method is to use Fibrin glue, which is made from a protein found in humans which stops bleeding. By sticking to the whole surface of the graft, it is thought that Fibrin glue may improve healing. It may have an important effect in patients who are more likely to have graft failure, such as those with poor circulation, smokers, or the elderly.

Fibrin glue has been approved by the Australian Federal Government for use in attaching skin grafts for a number of years. There is research already on using it for burns, but not in skin cancer.
The results of this research will be used by the study doctor Ekta Paw to obtain a Masters of Philosophy degree.

### 3. What does participation in this research involve?

Participation in this project does not change your surgery. For some patients not participating in the trial we may also use the glue, as it is already part of usual care.

If there are no reasons you cannot participate in the study, you will be randomised to either: staples and stitches to attach your graft; or to the group which has fibrin glue to attach the graft. Your surgery will proceed as normal and your follow up appointments will be the same as normal (one week and one month). The only difference is that we will ask some questions about your medical history; your post-operative pain; and we will take photographs of your graft. The photographs will not include anything identifiable, and will only be seen by researchers to assess how well your wound has healed.

This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids study doctors or participants jumping to conclusions. Safety of the research will be monitored by a data safety management committee. There is also a study steering committee who will continually monitor progress and any unexpected events as they occur.

There are no additional costs associated with participating in this research project, nor will you be paid.

### 4. What do I have to do?

You will have to attend your surgery date as per usual, and your follow up appointments which are the same as if you were not participating in the study. It is important you attend these appointments on time as it will help assess the effectiveness of the glue. You can continue all your regular medications.

### 5. Other relevant information about the research project

There will be 334 patients participating in this study, of which half will have the glue used, and half will have stitches or staples used. There are two hospitals in Townsville involved.

### 6. Do I have to take part in this research project?

 Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage. If you do decide
to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

7 What are the alternatives to participation?
If you don’t participate, your surgery will occur as usual, with the usual follow up. It is possible you may still have Fibrin glue used for your skin graft as it is part of the current standard of care.

8 What are the possible benefits of taking part?
We cannot guarantee or promise that you will receive any benefits from this research; however, possible benefits may include better healing of skin graft, less risk of infection, faster surgery and less pain after surgery. By taking part you may have an increase in the observation of your wounds and because of this problems or issues may be picked up faster. Taking part will enable doctors to know if this glue is truly better or not. If the glue is shown to improve outcomes, future patients may have better healing, less pain, less infections and need to attend hospital less often after having skin grafts.

9 What are the possible risks and disadvantages of taking part?
While Fibrin glue has been approved by the Australian Federal Government, there have been a small number of adverse outcomes reported which have been associated with its use. These have mainly related to hypersensitivity reactions to the proteins. It is for this reason that we will not allow people who have a known allergy to bovine protein to participate in this study. However, it is possible you may have an allergy without knowing about it previously. Allergy reactions can range from itchiness and redness, to difficulty breathing and a drop in blood pressure. While this is a very rare occurrence, if it does occur it will be within a very short time of exposure to the allergen (Fibrin glue), and you will be closely monitored during and after your surgery for any signs of this so it can be treated quickly.

10 What if I withdraw from this research project?
You are welcome to withdraw from this research project at any time if you no longer wish to be a participant. Your surgery and follow up will go ahead as usual, with no change to the timing or quality of your care. Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with Townsville Hospital/Mater Health Services North Queensland.

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the...
research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the sponsor up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

11 Could this research project be stopped unexpectedly?
This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as:

- Unacceptable side effects
- The treatment being shown not to be effective
- The treatment being shown to work and not need further testing

12 What will happen to information about me?
By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project will be that can identify you will remain confidential. Data will be kept in a form which does not identify you, but in case we need to re-identify a participant for medical reasons there will be a code. This code will be kept securely in a password protected electronic format which can only be accessed by the researchers involved in this study. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law. Data will be kept securely for 15 years following completion of the study as per James Cook University guidelines.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form you agree to the study team accessing health records if they are relevant to your participation in this research project.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission. Data will only be presented as numerical results with no identification of individual participants.
13 Complaints and compensation

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

14 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of Townsville Hospital.

This project will be carried out according to the National Statement on Ethical Conduct in Human Research (2007). This statement has been developed to protect the interests of people who agree to participate in human research studies.

15 Further information and who to contact

The person you may need to contact will depend on the nature of your query. If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor on 4433 1111 or any of the following people: Dr Mark Zonta, Dr Venkat Vangaveti.

Research Contact Person:
Name: Dr Ekta Paw
Position: Principal House Officer, General Surgery
Phone: 4433 1111
Email: ekta.paw@health.qld.gov.au

This project has been reviewed and approved by the Townsville Hospital and Health Service Human Research Ethics Committee. For concerns relating the conduct of this project contact:
HREC Chairperson
Phone: 07 4433 1440
Email: TSV-Ethics-Committee@health.qld.gov.au
PATIENT/PARTICIPANT CONSENT FORM

PROTOCOL NAME: Fibrin Glue in Skin Grafts for Skin Cancer (FiGSS)

INVESTIGATORS: Principal investigator Ekta Paw BSc MBBS

1. The nature and purpose of the research project has been explained to me. I understand it and acknowledge that taking part in this study is voluntary.

2. I have been given an Information Sheet which explains the purpose of the study, the possible benefits, and the possible risks.

3. I understand that I may not directly benefit from taking part in the trial.

4. I understand that, while information gained during the study may be published, I will not be identified and my personal results will remain confidential.

5. I understand that I can withdraw from the study at any stage and that it will not affect my medical care, now or in the future.

6. I have had the opportunity to discuss taking part in this investigation with a family member or friend.

NAME OF PARTICIPANT: ____________________________

SIGNATURE: ____________________________

DATED: ____________________________

I certify that I have explained the study to the patient/volunteer and consider that he/she understands what is involved.

NAME OF PRINCIPAL INVESTIGATOR: Dr Ekta Paw

SIGNATURE: ____________________________
# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

| Reporting Item | Page Number |
|----------------|-------------|
| Title          | #1          | 1 |
| Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym |
| Trial registration | #2a | 2 |
| Trial identifier and registry name. If not yet registered, name of intended registry |
| Trial registration: dataset | #2b | 10 |
| All items from the World Health Organization Trial Registration Data Set |
| Protocol version | #3 | 4 |
| Date and version identifier |
| Funding | #4 | 10 |
| Sources and types of financial, material, and other support |
| Roles and responsibilities: contributorship | #5a | 1 |
| Names, affiliations, and roles of protocol contributors |
Roles and responsibilities: sponsor contact information

Roles and responsibilities: sponsor and funder

Roles and responsibilities: committees

Introduction

Background and rationale #6a Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention

Background and rationale: choice of comparators #6b Explanation for choice of comparators

Objectives #7 Specific objectives or hypotheses

Trial design #8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting #9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained

Eligibility criteria #10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will...
perform the interventions (eg, surgeons, psychotherapists)

Interventions: description
#11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered

Interventions: modifications
#11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)

Interventions: adherence
#11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)

Interventions: concomitant care
#11d Relevant concomitant care and interventions that are permitted or prohibited during the trial

Outcomes
#12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended

Participant timeline
#13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)

Sample size
#14 Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations

Recruitment
#15 Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation: sequence generation
#16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
Allocation concealment mechanism  
Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned.

Allocation: implementation  
Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions.

Blinding (masking)  
Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how.

Blinding (masking): emergency unblinding  
If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial.

Methods: Data collection, management, and analysis

Data collection plan  
Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol.

Data collection plan: retention  
Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols.

Data management  
Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol.

Statistics: outcomes  
Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol.

Statistics: additional analyses  
Methods for any additional analyses (e.g., subgroup and adjusted analyses).
Statistics: analysis population and missing data

Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

Methods: Monitoring

Data monitoring: formal committee

Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

Data monitoring: interim analysis

Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial

Harms

Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct

Auditing

Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval

Plans for seeking research ethics committee / institutional review board (REC / IRB) approval

Protocol amendments

Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)

Consent or assent

Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)

Consent or assent: ancillary studies

Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

Confidentiality

How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
| Section                                      | Code | Text                                                                                                                                                                                                 |
|----------------------------------------------|------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Declaration of interests                     | #28  | Financial and other competing interests for principal investigators for the overall trial and each study site                                                                                           |
| Data access                                  | #29  | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators                                                         |
| Ancillary and post trial care                | #30  | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation                                                                             |
| Dissemination policy: trial results          | #31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions |
| Dissemination policy: authorship            | #31b | Authorship eligibility guidelines and any intended use of professional writers                                                                                                                        |
| Dissemination policy: reproducible research   | #31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code                                                                                       |
| Appendices                                   |      |                                                                                                                                                                                                      |
| Informed consent materials                   | #32  | Model consent form and other related documentation given to participants and authorised surrogates                                                                                                     |
| Biological specimens                         | #33  | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable |

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