Protocol for a Systematic Review of Outcomes From Microsurgical Free Tissue Transfer Performed on Short-term Surgical Missions in Low-income and Middle-income Countries

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Protocol

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Abstract

Background: In many units around the world, microsurgical free tissue transfer represents the gold standard for reconstruction of significant soft tissue defects following cancer, trauma or infection. However, many reconstructive units in low-income and middle-income countries (LMICs) do not yet have access to the resources, infrastructure or training required to perform any microsurgical procedures. Long-term international collaborations have been formed with annual short-term reconstructive missions conducting microsurgery. In the first instance, these provide reconstructive surgery to those who need it. In the longer-term, they offer an opportunity for teaching and the development of sustainable local services.

Methods: A PRISMA-compliant systematic review and meta-analysis will be performed. A comprehensive, predetermined search strategy will be applied to the MEDLINE and Embase electronic databases from inception to December 2020. All clinical studies presenting sufficient data on free tissue transfer performed on short-term surgical missions (STSMs) in LMICs will be eligible for inclusion. The primary outcomes are rate of free flap failure, rate of emergency return to theatre for free flap salvage and successful salvage rate. The secondary outcomes include postoperative complications and any functional or patient reported outcome measures. Screening of studies, data extraction and assessments of study quality and bias will be conducted by two authors. Individual study quality will be assessed according to the Oxford Evidence-based Medicine Scales of Evidence 2, and risk of bias using either the 'Revised Cochrane risk of bias tool for randomized trials' (Rob2), or the 'Risk of bias in non-randomized studies of interventions' (ROBINS-I) tools. Overall strength of evidence will be assessed according to the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach.

Discussion: To-date the outcomes of microsurgical procedures performed on STSMs to LMICs are largely unknown. Improved education, funding and allocation of resources are needed to support surgeons in LMICs to perform free tissue transfer. STSMs provide a vehicle for sustainable collaboration and training. Disseminating microsurgical skills could improve the care received by patients living with reconstructive pathology in LMICs, but this is poorly established. This study sets out a robust protocol for a systematic review designed to critically analyse outcomes.

Systematic review registration: Submitted to PROSPERO (15/12/20 ID: 225613)

Background

Five billion people around the world are living without access to adequate surgical care(1). Short-term surgical missions (STSMs) provide an opportunity for surgical teams from higher-income nations to collaborate with surgeons from low-income and middle-income countries (LMICs) to treat those most in need. Historically, some STSMs have been criticised for an unsustainable 'fly-in-fly-out' model of surgical care delivery in LMICs, with limited patient follow-up after discharge. One consequence of this approach is a poor evidence base by surgeons working in resource-limited settings are able to decide on the best

treatment options for their patients.(2). However, most STSMs return annually to the same centre, building lasting relationships, offering sustainable education and training, and treating patients who would otherwise have no access to healthcare. This model offers greater opportunity for thorough follow-up. Indeed, new methods of long-term patient follow-up after discharge are emerging that aim to improve patient safety after STSMs in LMICs(3, 4).

Free-tissue transfer can be considered the gold-standard method of reconstruction after significant composite tissue defects from cancer, trauma and infections(5–8). In the largest series from high volume centres, flap failure rates as low as 0.6 %, and take back rates of of 1.5% (66 % successful salvage rate) have been published(9). For surgeons operating in LMICs, that do not have funding and access to the required equipment and training to facilitate independent microsurgical practice, treatment options are restricted to those used 50 years ago in countries that now perform regular free tissue transfer. For select advanced pathology, this may be the difference between amputation and lower limb salvage after trauma and sarcoma resection, or poorer functional outcomes following head and neck cancer reconstruction(10–14). Performing microsurgery in LMICs is challenging, even for experienced teams. However, a select few centres in LMICs are undertaking these procedures as part of standard practice(15–17). Local and regional alternatives do exist, however many of these are also technically demanding, and even with extensive training, microsurgical equipment and techniques, they are vulnerable to complications requiring further surgery(18–21). However, there is also some data in support of successful local reconstructive alternatives being used effectively in low-resource contexts(21).

There are some fundamental challenges to providing microsurgery in LMICs. Amongst those reported are a lack of specialist equipment, trained staff and appropriate level three post-operative monitoring facilities(22). STSMs, which can provide additional staff and resources, can directly address these challenges. However, these are usually short-term interventions, and patients may not be afforded the same degree of follow-up provided by the home institutions of the visiting surgeons. In addition, it is traditionally held that reconstructive surgeons should stick to ‘simple’ surgery on STSMs(23). Therefore, it is important to establish the safety of delivering free tissue transfer on STSMs. Identification of common complications and constraints will inform organisations engaged in STSMs where to focus their training and fundraising efforts in order to improve patient outcomes.

The aim of this study is to publish a robust systematic review protocol to establish the safety and efficacy of microsurgical free tissue transfer performed on STSMs in low-income and middle-income countries.A meta-analysis of key outcomes will be undertaken with the aim of developing potentially life changing microsurgical practice in resource-limited settings.

Methods

This protocol is registered on the PROSPERO international prospective register of systematic reviews (Submitted 15/12/20 ID: 225613) and is written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) guidelines (24, 25). The methodology

applied to the final systematic review and meta-analysis is derived from, and in line with, the Cochrane Handbook for Systematic Review of Interventions(26) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (27).

Search strategy

The search strategy (Table 1) will be applied to the MEDLINE and Ovid EMBASE databases from inception to 2nd January 2021.

Table 1.

Electronic database search – MEDLINE and Ovid EMBASE

	Concept 1 – Surgery	**AND**	**Concept 2 – Micro**	**AND**	**Concept 3 – STSM**
MeSH term	**Surgery**		**Free Tissue Flaps**		**Medical Missions**
OR			**Microsurgery**		
		OR	Flap*	**OR**	Mission*
		OR	Free Flap*	**OR**	Humanitarian
		OR	Free Tissue Transfer	**OR**	Visit*
				OR	Charit*
				OR	Trip
				OR	Outreach
				OR	Volunt*
				OR	Non-government*
				OR	Safari
				OR	Blitz
				OR	Camp

Study selection criteria

Inclusion criteria

All clinical studies reporting outcomes of any microsurgical procedure performed on a short-term reconstructive mission to any low-income or middle-income country (in accordance with the world bank classification(28)) will be eligible for inclusion. Studies that match the inclusion criteria performed in low-resource environments in a high-income country will also be included. Children and adults will be considered. All cases performed using either operating microscope or loupe magnification will be

included, as both are successfully reported in resource-limited settings(15). The Population, Intervention, Comparison, Outcome (PICO) model was used to determine study selection criteria (Table 2)(29).

Table 2.

Population, Intervention, Comparison, Outcome (PICO)

Population	Intervention	Comparator	Outcomes
Patients operated on during STSMs	Reconstructive surgery by microvascular free tissue transfer	Data from the UK National Flap Registry(8)	Rate of complications
In low- and middle-income countries or low-resource health environments	Performed during a visiting surgical mission		Nature of complications
Children and adults to be included	This will include both loupes and microscope magnification		Rate of return to theatre
			Rate of free flap salvage
			Nature of attempted salvage

Exclusion criteria

Studies that do not provide sufficient data for comparative analysis will be excluded. Where incomplete or absent data is presented in a given study, study authors will be contacted by email on a maximum of two separate occasions, two weeks apart, inviting them to provide further data before being excluded. Data presented from microsurgical units already independently performing microsurgery in low-income or middle-income countries, not on a STSM, will also be excluded.

Study design

Randomised controlled trials (RCTs), cohort, case-control and case series will be considered for inclusion. Pilot searches indicate that the majority of studies will be case series of varying sizes. As such, no limitation regarding study size or clinical follow-up will be made. Case reports, letters, opinion pieces and literature reviews will be excluded. Any unpublished or ongoing prospective clinical trials will also be excluded.

Participants

Children or adults that have undergone microsurgical free tissue transfer during a short-term surgical mission in a low-income and middle-income country. No limitations based on patient demographics, body

region or aetiology will be imposed.

Outcomes

Primary outcomes

The primary outcomes are rate of free flap failure and rate of emergency return to theatre for attempted free flap salvage. Return to theatre will be classified as a donor site or anastomotic complication. The time taken to return to theatre, and the rate of successful flap salvage will also be documented where available. Where disclosed, we will record the method of flap salvage attempted.

Secondary outcomes

The secondary outcomes will include complications and any functional or patient reported outcome measures included. Based on previous large case studies of free flaps, complications will be divided into medical and surgical. The surgical group will be further subdivided into intraoperative and post-operative. Complications will be stratified according to the Clavien-Dindo classification(30–32). Finally, if available any assessment of pre-operative fitness will be recorded.

Additional data

In addition to the primary and secondary outcomes, duration of procedure and length of stay will also be recorded where available. In the context of a STSM to a LMIC, this is particularly important. The following will also be extracted: bibliographic data (Title, author, date), study characteristics (design, method of randomisation/allocation, blinding, number of participants, groups/subgroups), mission characteristics (country, length of mission, type of mission/subspecialty, organisation (type and size), type of hospital (e.g. public or private), frequency of missions), patient characteristics (age, sex, indication for surgery, comorbidities, smoking status), intervention characteristics (Operation(s) performed, duration of operation, length of stay, who performed the surgery (local or visiting surgeon), experience level of surgeon who performed anastomosis and raised flap, pre-operative workup), and rate and duration of follow up.

Outcomes will be compared to data available from the multicentre, UK National Flap Registry, published in 2019(8).

Data management and extraction

Abstracts will be screened on the Rayyan systematic review software tool. Full papers will be downloaded as PDFs, and stored locally on Mendeley Desktop. All abstracts included will proceed to full text analysis unless it is immediately apparent following reading of the introduction that they are irrelevant. Data items will be collected in a standardised data collection proforma. For instances of incomplete data, we will contact the corresponding author. If 2 weeks elapse with no response, we will repeat this request once.

Data selection

Screening will be conducted and recorded in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines(27). Abstracts screened according to criteria set out in this protocol by two independent researchers (HdB and UC). In case of disagreements: researchers will meet to discuss disparities; if there are still disagreements, a third author (CH) will make the final decision on inclusion. If abstracts are not available on assessment, the paper will be downloaded in full for analysis.

Risk of bias assessment

Each study will be assessed for risk of bias by two independent reviewers (HdB and UC) according to an appropriate validated tool. Randomised studies will be assessed using the revised Cochrane risk of bias tool for randomized trials (Rob2)(33). Non-randomised studies will be assessed using the 'Risk of bias in non-randomized studies of interventions' (ROBINS-I) tool(34).

Quality of studies

Each study will be assessed according to the Oxford Evidence-based Medicine Scales of Evidence 2(35). This data will be tabulated.

Strategy for data analysis and synthesis

Statistical analysis of included studies will be undertaken in Revman 5.4 (Cochrane Collaboration, Oxford, United Kingdom). Patient demographics will be presented using basic descriptive statistics. Complications, free flap failure, emergency return to theatre and successful free flap salvage will be calculated and displayed as rate (%). Data from the first UK National flap registry will be used as a comparator(8). Statistical heterogeneity will be examined by calculating I^2 and Cochran's Q statistic, and interpreted according to Cochrane guidance on determining heterogeneity(26). If $I^2>50$, a random-effects model (DerSimonian and Laird with a logit transformation applied) will be used to calculate relative risk with 95% confidence intervals(36). If $I^2 \leq 50$, a fixed-effects model will be used for relative risk calculations. A *p*-value of <0.05 will be considered statistically significant. The results of this meta-analysis will be presented in Forest plots. Funnel plots will be used to detect publication bias. If quantitative analysis is inappropriate a narrative synthesis will be performed.

The analysis detailed above will be undertaken for the pooled data. If sufficient data is available, subgroup analysis by region (e.g. head and neck, trunk etc.) will be undertaken.

Confidence in cumulative evidence

The body of evidence underpinning each of the findings will be assessed according to the 'Grading of Recommendations, Assessment, Development and Evaluations' (GRADE) approach(37). Using this approach, the authors will express their 'certainty' that the body of evidence reflects reality (High, moderate, low, very low).

Discussion

This will be the first systematic review and meta-analysis of the outcomes of free tissue transfer performed on STSMs to low-income and middle-income countries. Our pilot searches indicate that the majority of data will be published in case series', it is difficult to form a conclusion from any one of these alone. This underlines the importance of a thorough synthesis of these studies into a unifying review article. However, lack of randomised allocation and control groups increase the risk of bias, and this has led to concerns regarding the quality of evidence in this field(38). We cannot remedy this, but will provide the reader with an open appraisal of the body of evidence according to the GRADE approach. From this they will be able to form their own conclusions about their confidence in our findings.

We predict considerable clinical heterogeneity between the studies included in this paper. STSMs are often based on relationships between specific institutions, sometimes individual surgeons, and thus there is no 'one size fits all approach'. Another source of heterogeneity will come from the inclusion of all flap types. We will try to mitigate this through sub-group analysis if possible, but there may be insufficient data available.

Nutritional status has been identified as a determinant of free flap outcome(39). STSMs treat a diverse population of patients, many of whom will have poor nutritional status. This may be a confounding factor in reconstructive outcomes, but is unlikely to be well documented in a standardised manner across the literature. We will collect nutritional and other preoperative assessments where possible, but there may not be sufficient data to adjust for these variables.

We hope to equip surgeons undertaking STSMs with the relevant data to offer appropriate treatment to their patients in order to achieve the best possible outcomes. In addition, this will ensure patients are able to give informed consent with an understanding of the risks specific to their situation. These impacts will improve patient safety, reconstructive outcomes and follow-up.

Finally, with appropriately strict governance surrounding distribution of funds designed to provide healthcare in low- and middle-income countries, it is essential that actors in this field are able to provide evidence supporting their work. Through identifying the nature and severity of complications, we hope to inform surgeons and funders of the challenges and barriers to free tissue transfer in LMICs. This should encourage investment in areas that are most likely to improve patient outcomes. This study will assist those funding global surgery to allocate resources to appropriate interventions with proven patient benefit.

Abbreviations

EMBASE Elsevier Biomedical and Pharmacological Bibliographic Database

GRADE Grading of Recommendations, Assessment, Development and Evaluations

LMICs Low- and Middle-Income Countries

MEDLINE US National Library of Medicine Bibliographic Database

MeSH Medical Subject Headings

PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO International prospective register of systematic reviews

RCT Randomised controlled trial

Rob2 Revised Cochrane risk of bias tool for randomized trials

Robins-I Risk of bias in non-randomized studies of interventions

STSM Short-Term Surgical Mission

Declarations

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Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests

All of the authors have volunteered for the non-governmental organisation Project Harar, which conducts STSMs. VP and MM are trustees for Project Harar, and both sit on the board of directors

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Authors' contributions

All of the listed authors have made a substantial contribution toward the development of this protocol. CH conceived the study, reviewed the protocol design and registration, took part in the manuscript drafting and completion and gave specialist input relating to microsurgery and STSMs in LMICs. HdB developed the search strategy and data analysis section, reviewed the protocol design and registration, took part in the manuscript drafting and completion. DB,VP, MB, FA, GW, MM, DM, ME and VP provided expertise in the methodology and clinical area covered. HdB, UC developed the search strategy and data extraction policy. HdB established the statistical approach contained within this protocol. All authors also drafted and edited the manuscript and approved the final version prior to submission.

All authors act as guarantors of this protocol.

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