Which outcomes should we measure in cellulitis trials? Results of a systematic review of outcomes included in cellulitis trials and a patient priority setting survey

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Sponsor/funding information?

Anticipated start date: 24 April 17
Anticipated completion date: 31 July 17
Funding sources/sponsors:
Conflicts of interest: None known

Introduction

I. Rationale

Cellulitis is a bacterial infection of the dermis and subcutaneous layers of the skin. If left untreated, it can have serious consequences for the health and wellbeing of patients. Despite being a readily-treatable disease, recurrence rates are high and little is known about the effects of the cellulitis, both in the short and long-term (Raff, 2016).

An area of particular concern is the measurement of outcomes of cellulitis in randomised controlled trials that assess treatment and prevention. Research suggests that outcome scales may not be measuring actual improvements following cellulitis treatment due to a limited focus on factors such as fever, biochemical markers and visible extent of area of infection (Montalto, 2013). Clinicians often rely on direct inspection of the skin to assess severity and improvement, which is not only highly subjective, but is difficult to standardise due to poor reliability and validity (Montalto, 2013). In addition, it devalues patient experience of disease improvement, which can vary significantly from clinician perspectives (Simpson, 2013). Choice of therapeutic intervention is most often driven by patient-reported symptoms in response to treatment (Simpson, 2013); therefore an emphasis on patient-focused outcomes is important.

Selecting and defining a standard set of outcomes is integral for the design of reliable clinical trials. Essentially, they need to be relevant to health service users and clinicians if the research is going to influence future practice (Kirkham, 2015). There is a move towards creating core outcome sets (COS) for skin conditions: an agreed set of well-defined outcomes which should be used in all clinical trials (Kirkham, 2015). The Harmonising Outcome Measures for Eczema (HOME) initiative has set out a core set of outcome domains for this very purpose (Schmitt, 2014). The aim of this process is to ensure treatment effects are being measured accurately and reliably across all trials and that patient-reported outcomes are given sufficient weight. Furthermore, they aim to facilitate the conduct of systematic review and meta-analyses in order that treatment efficacy and cost-benefit can be directly compared (Schmitt, 2014). Identifying the types of outcome measures included in trials and exploring patient and health practitioner perspectives is therefore an important first step in facilitating the development of valid, reliable and disease-specific outcome measures which can be used for assessment across all trials.

Of the limited number of cellulitis trials conducted, there has yet been no systematic review of the types of outcome measures being used, how they are measured and by whom, scales used and how they vary across trials. Moreover, little is known about patient experiences of the effects of cellulitis and outcome measures patients and health practitioners would like to see included in future trials (Carter, 2007).

Therefore, for purposes of gathering evidence that can assist researchers in making informed decisions regarding the most appropriate measures to use in future trials, this study will utilise a mixed methods design to map information about outcome measures used in published randomised controlled trials of cellulitis treatments, and to explore patient and health practitioner perspectives on outcomes of interest.

II. Objectives

Primary objective

- To systematically review and compare outcome measures used in published randomised controlled trials of the treatment or prevention of cellulitis

Secondary objective

- To explore patients' and health practitioners' perspectives on cellulitis outcomes they would like to be measured in future trials using data extracted from the Cellulitis Priority Setting Partnership (PSP).

Methods

This study will employ a mixed methods design to address the study objectives. The first phase of this project will consist of a systematic review of outcome measures in intervention studies of cellulitis; the second phase will consist of extracting patient and clinician perspectives on outcomes of importance from the Cellulitis Priority-Setting Partnership.

Study 1: Systematic review design

Aim

Review all outcomes included in randomised controlled trials from two Cochrane reviews on treatment and prevention of cellulitis, specifically focusing on: what is being measured, how the outcome measure is defined and similarities or variations in outcomes across trials.

Search strategy

Randomised-controlled trials from two recent (2016) Cochrane reviews: "Interventions for the treatment of cellulitis and erysipelas" and "Interventions for the prevention of recurrent erysipelas and cellulitis" will be screened for inclusion.

There will be no language restriction, all studies relating to treatment or prevention of cellulitis will be screened.

Eligibility criteria

Inclusion criteria

- RCT assessing effects of treatment for acute episodes of cellulitis/erysipelas (or skin and soft tissue infections)
- RCT assessing prevention of recurrence of cellulitis/erysipelas
- Adult patients
- Full text articles, published in peer reviewed journals

Exclusion criteria

Data on patient safety will not be extracted, as such, data reporting adverse effects or side effects of medication will not be gathered, as this is routinely monitored in RCTs and are not directly relevant to our research question.

Data collection and management

Full text articles will be reviewed and the following data will be extracted and listed for each trial in an Excel file (FT=free-text, DD=drop-down box):

- Name of first author
- Year of trial publication
- Country
- Whether trials assess treatment of acute cellulitis or the prevention of recurrence (DD)
- Whether trial is drug/non-drug intervention

All outcome measures listed in the methods section will be reported, with the following details:

- Whether primary outcomes are stated (Y/N)
- Total number of outcomes measured per trial
- Whether outcomes are in line with FDA/EMA guidance (Y/N)
- Additional comments on outcomes e.g. justification of outcome used (FT)
- Broad outcome domains (DD /FT):
    - *Clinical outcome* e.g cure/ recurrence
    - *Microbial outcome* e.g eradication/ persistence
    - *Biochemical outcome* e.g WCC, CRP
    - *Treatment-related outcome* e.g length of antibiotic therapy
    - *Patient-focused outcome* e.g treatment satisfaction
    - *Additional outcomes* e.g length of hospital stay
- Definition of each outcome domain (FT)
- For "clinical outcomes", specific clinical features will be defined, for example: erythema, pain, swelling, temperature (DD/FT)
- Scales or categories used for each outcome (e.g. '0, none; 3, excellent') (FT)
- Who outcome is assessed by (nurse, clinician, patient, other) (DD/FT)
- How outcome was assessed (i.e. indelible marker) (FT)
- Timing/ frequency of assessment (FT)

The primary data extractor will be ES. Secondary data extractor will be MP. KT will oversee review, offer feedback on specific queries and act as 3rd reviewer if disagreements between ES + MP.

Study 2: Extracting feedback from the Cellulitis Priority Setting Partnership

Aim

Capture data on the types of outcomes patients/carers/health professionals feel are important for cellulitis trials and compare these to the outcomes currently being captured in published clinical trials

Method

- ES will analyse the participant feedback on priorities for research from the PSP using data stored in an Access file.

- Outcome themes will be extracted from the statements and each statement will be numerically coded as an "outcome".
- The data extracted and analysed as below

Data collection and management

Data from the PSP will be downloaded into an Excel file and the following steps of data analysis will occur:

- Data concerning treatment outcomes will be separated into broad outcome domains as described for study 1.
- Demographics of the individuals giving feedback will be noted e.g type of responder, demographic details if available

Data synthesis

- The percentage of total outcome statements which correspond to each domain will be calculated.
- Comparisons between themes identified in the PSP and those measures reported in trials will be made.
- Outcome measures extracted from systematic review and PSP will be presented in tables and qualitatively reported in the results section.

Ethical considerations

As the primary purpose of this survey is to explore patient and health practitioner perspectives on research priorities, patient or public involvement in research therefore does not require ethical approval.

Dissemination

Results of the study will be disseminated by email to participants of the PSP and details added to the CEBD website. The final report will be submitted for publication.

Conclusions

The primary purpose of this mixed methods study is to address a number of gaps concerning the measurement of outcomes in cellulitis trials assessing treatment effects. It is expected that identifying the types of outcomes being used as well as exploring patient and health practitioner perspectives will facilitate researcher decisions regarding the most appropriate and important outcomes for cellulitis. The research should be a step towards identifying a core outcomes set for future cellulitis trials.

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