Coordinated Research Infrastructures Building Enduring Life-science services
- CORBEL -

Deliverable D3.6
Assessment of animal model phenotypes against outcome measures

WP3 – Community-driven cross-infrastructure joint research - Medical

Lead Beneficiary: ECRIN-ERIC
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Contributing partner(s): ECRIN, U Liverpool, VU/VUMC, INFRAFRONTIER

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Executive Summary

Animal models play a crucial role in understanding the mechanisms of diseases and symptoms, and to test the efficacy and safety of treatments before conducting clinical trials. Selecting human diseases and developing core sets of clinical outcome measures as well as complementary sets of mouse phenotyping measures will contribute to narrow the gap between animal models and human trials.

The overall objective of the CORBEL task 3.2 is to promote convergence between outcome measures used for clinical trials in humans and phenotyping techniques used for testing treatments in animal models.

Project objectives

With this deliverable, the project has reached/this deliverable has contributed to the following objectives:

a) Development of a core outcome set for the model disease (type 2 diabetes)
b) Development of a protocol to identify outcomes used in pre-clinical studies of interventions to reduce glycaemia in mouse models of type 2 diabetes.
c) Identification of relevant pre-clinical studies using a mouse model for type 2 diabetes for the comparison of outcomes used against the core outcome set.
d) Development of a protocol and identification of research studies assessing quality of life, fatigue and wellbeing in mouse models of disease.
e) Review of the Methods used in the selection of instruments for outcomes included in Core Outcome Sets

Detailed report on the deliverable

Background

Mice are widely used in biomedical research to gain insight to the gene function in human health and diseases, to act as disease models to elucidate the involved pathways and the effects of treatments, and to support the development of (genome-based) treatments for human diseases. However, there is a need to improve translation from pre-clinical work to later phase human interventions. Reviewing the outcomes used and developing a complementary set of mouse phenotyping assays and of clinical outcomes for specific diseases, in this case type 2 diabetes, will contribute to improve the predictive value of the mouse model and the translation of pre-clinical research.

Also, quality of life, fatigue and wellbeing are life impact measures that are important to patients and are normally measured by self-reporting. Assessing these outcomes with specific tests in murine models of disease will mimic human clinical trials aiding in translatability.

Description of Work

1. **Comparison of outcomes used in pre-clinical studies and phase 3/4 effectiveness trials.**
   The SCORE-IT core outcome set for type 2 diabetes has been developed and published (see "publications") and these core outcomes will now be considered in a pre-clinical setting. A protocol for the identification of relevant pre-clinical studies has been published in the PROPSERO database[1].
   The searches, abstract and full text screening, and outcome extraction have been completed (see Appendix 1: PRISMA diagram). The outcomes will be compared to those identified in the review of registered phase3/phase4 studies. A paper will be written and submitted for publication.
2. **Patient reported outcome measures (PROMs) for type 2 diabetes**
   The SCORE-IT core outcome set represents "what" should be measured but attention also needs to be given to "how" each outcome should be measured. A systematic review of all PROMs for diabetes type 2 has been completed and will describe the content of all PROMs that have specifically been developed or validated to measure (aspects of) health related quality of life (HRQL) in adults with type 2 diabetes. Based on the reviews described above we will provide recommendations for how to measure 'activities of daily living', one of the core outcomes of the diabetes COS.
   Work is also underway on how to measure 'global quality of life', the second patient-reported core outcome in the diabetes COS. A systematic search on the PROMIS Global02 item has been completed and the evidence on the measurement properties of this single item has been summarized. . Next step is to reach consensus on the proposed recommendations.
   In addition a review of the Methods used in the selection of instruments for outcomes included in Core Outcome Sets has been completed and will be submitted for publication.

[1] https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=106831

3. **Assessment of quality of life, fatigue and wellbeing in mouse models of disease**
   The aforementioned SCORE-IT core outcome set for type 2 diabetes includes global quality of life (someone's overall quality of life including physical, mental and social wellbeing) and activities of daily living. These outcomes are normally assessed using questionnaires (self-reports) completed by patients engaged in drug-testing clinical trials from a wide array of human diseases (not only in the context of type 2 diabetes). As an extension of the "how to measure" mapping effort in humans, our aim is to systematically review those methods/tests that measure quality of life, fatigue and wellbeing in mouse models of disease. The protocol for the review has been registered in the PROSPERO database2.
   Two reviewers have independently finished screening the 5083 abstracts retrieved after searching for articles in MEDLINE (via PubMed) and Web of Science. Due to the high number of abstracts for full text screening, it was agreed among the three reviewers to narrow the systematic review temporal window to the last ten years. This resulted in 890 articles that were included for full text screening and are currently being reviewed.

Next steps

1. **Comparison of outcomes used in pre-clinical studies and phase 3/4 effectiveness trials.**
   The next step for this activity is to summarize the results and submit a paper for publication in an academic journal. The slide set presented at the ICTMC conference will also be updated with the study to provide a useable set of reference slides.
2. **Patient reported outcome measures for type 2 diabetes.**
   Two manuscripts are in preparation:
   - The systematic review of all PROMs for type 2 diabetes
   - A systematic evaluation of the content validity of diabetes-specific PROMs that have been specifically developed to measure (aspects of) health-related quality of life in adults patients with type II diabetes, and that were validated to at least some extend.

   These activities will contribute to "how" the "activities of daily living" and "global quality of life" outcomes should be assessed. A further Delphi will seek consensus on these recommendations.
3. **Assessment of quality of life, fatigue and wellbeing in mouse models of disease**
   After screening a portion of the full text articles from our systematic review for assessment of quality of life, fatigue and wellbeing in mouse models of disease, it seems clear that a considerable fraction of these are related to fatigue. We have found that the number of methods/tests described for measuring quality of life, fatigue and wellbeing in mouse is vast and a lack of standardization is apparent. Thus, it may be sensible to aim for two manuscripts: one focusing on quality of life and wellbeing, and once completed, put our efforts on another systematic review dedicated exclusively to fatigue.

[2] https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=103507

Publications

- Selecting Core Outcomes for Randomised Effectiveness trials In Type 2 diabetes (SCORE-IT): a patient and healthcare professional consensus on a core outcome set for type 2 diabetes. BMJ Open Diabetes Research & Care 2019-12 DOI: 10.1136/bmjdrc-2019-000700[3]
- Incorporating patients' perspectives into the initial stages of core outcome set development: a rapid review of qualitative studies of type 2 diabetes. BMJ open diabetes research & care 2019-02 DOI: 10.1136/bmjdrc-2018-000615[4]
- SCORE-IT (Selecting Core Outcomes for Randomised Effectiveness trials In Type 2 diabetes): a systematic review of registered trials. Trials 2017-12 DOI: 10.1186/s13063-017-2317-5[5]
- PS5C -O5MOUSE –Mapping OUtcomes measured in pre-clinical Studies against randomised phase 3/4 Effectiveness trials. Oral presentation at the 5th International clinical Trials Methodology Conference[6].

Abbreviations

- PROMs: Patient Reported Outcome Measures
- HRQL: Health Related Quality of Life

Delivery and schedule

The delivery is delayed: No

Adjustments made

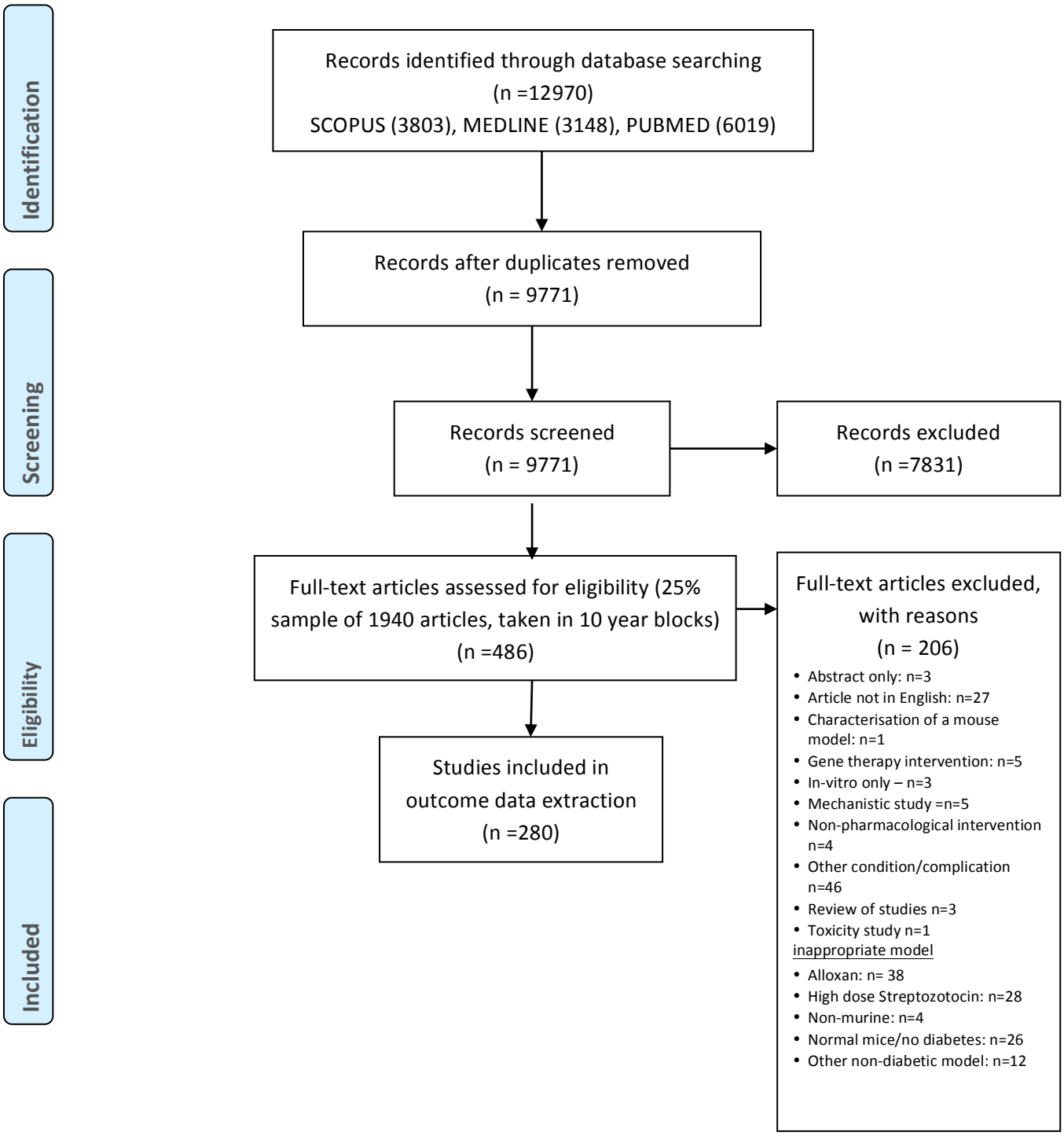
N/A

[3] http://dx.doi.org/10.1136/bmjdrc-2019-000700
[4] http://dx.doi.org/10.1136/bmjdrc-2018-000615
[5] https://doi.org/10.1186/s13063-017-2317-5
[6] https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-019-3688-6

Appendices

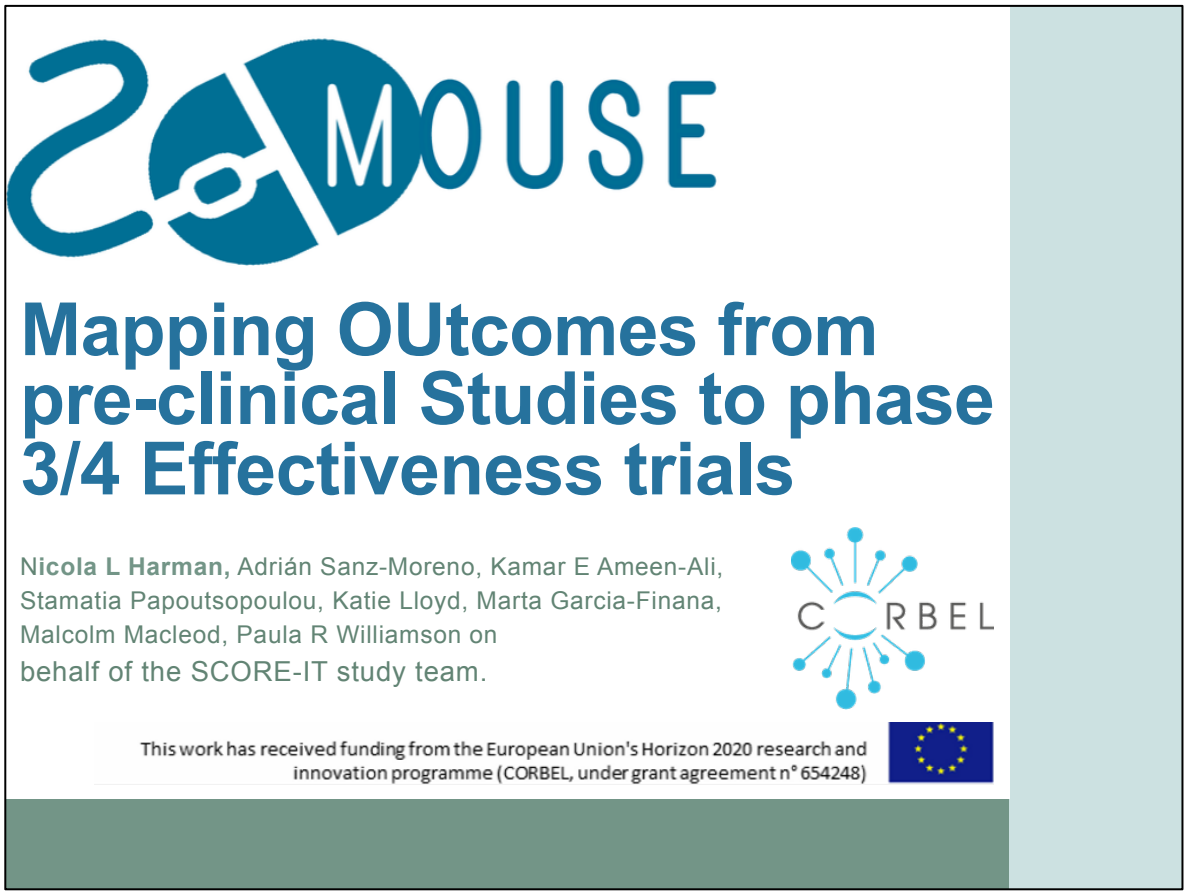
Appendix 1

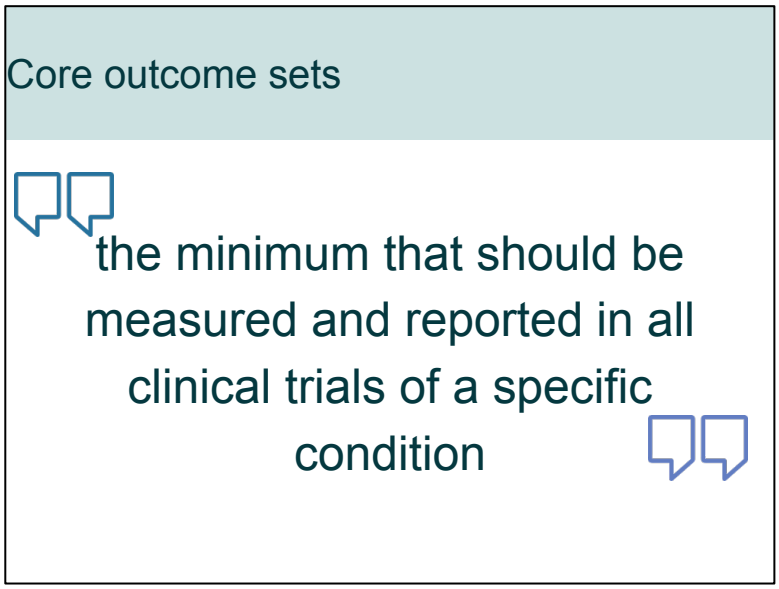
Figure 1. PRISMA Flow Diagram



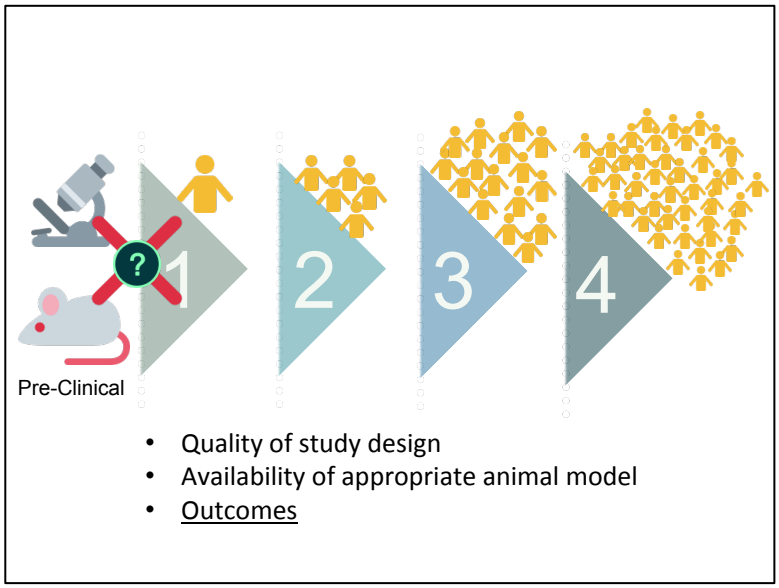
Appendix 2

PPT: ICTMC slide set to accompany PS5C -O5MOUSE –Mapping OUtcomes measured in pre-clinical Studies against randomised phase 3/4 Effectiveness trials. Oral presentation at the 5th International clinical Trials Methodology Conference.






Effectiveness trials
Early phase trials
Pre clinical studies


?
1
2
3
4
Pre-Clinical
Quality of study design
Availability of appropriate animal model
Outcomes


Outcomes that are important to patients, clinicians, researchers and policymakers at all stages of research.

Aims and objectives

Systematically review outcomes used in pre-clinical (in-vivo) studies of anti-diabetic interventions.

Compare pre-clinical outcomes with outcomes identified from a systematic review of phase 3/4 studies and a core outcome set .

SCORE-iT

SCOPE

METHOD

SCORE-iT

Core outcome set developed for adults with type 2 diabetes

Any intervention directed at blood glucose

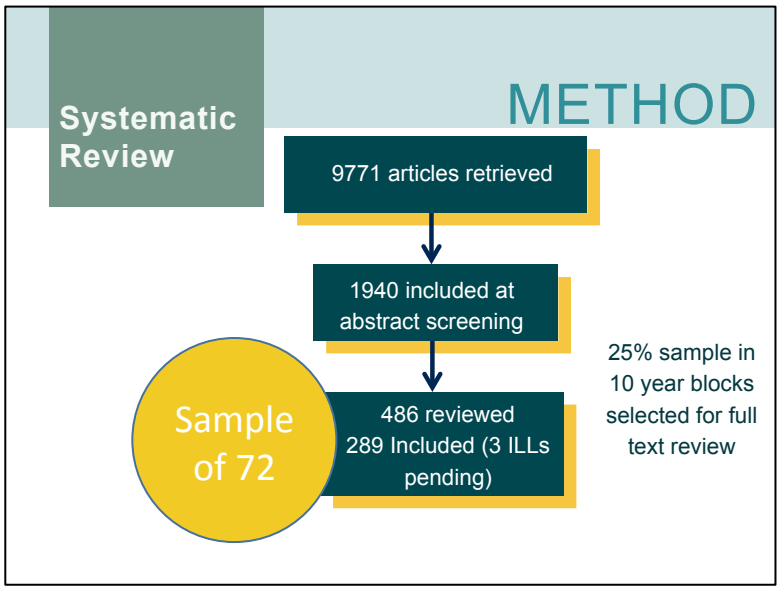
18 outcomes included in the COS.

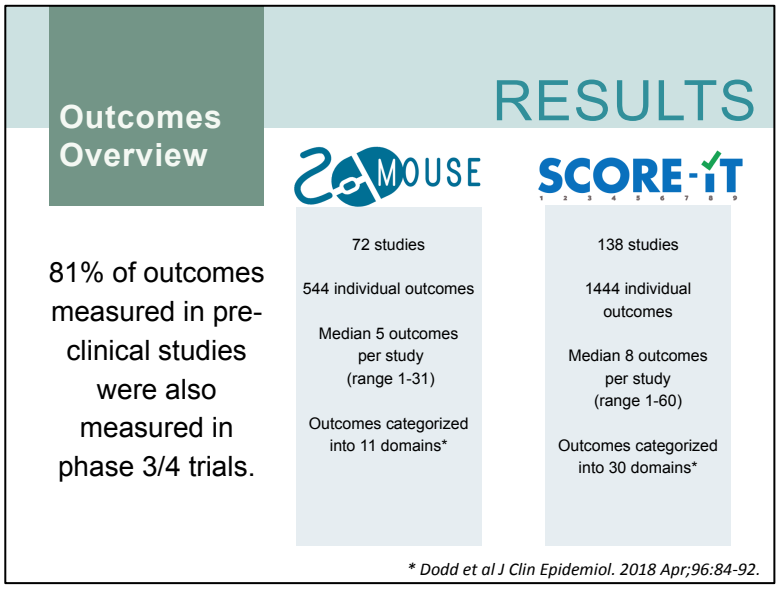
Harman *et al* BMJ Open Diabetes Research and Care, In Press

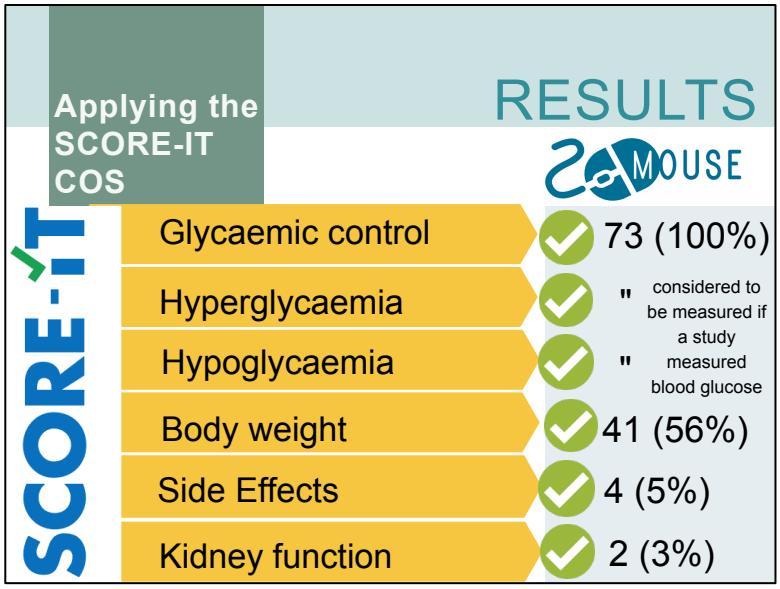
SCOPE

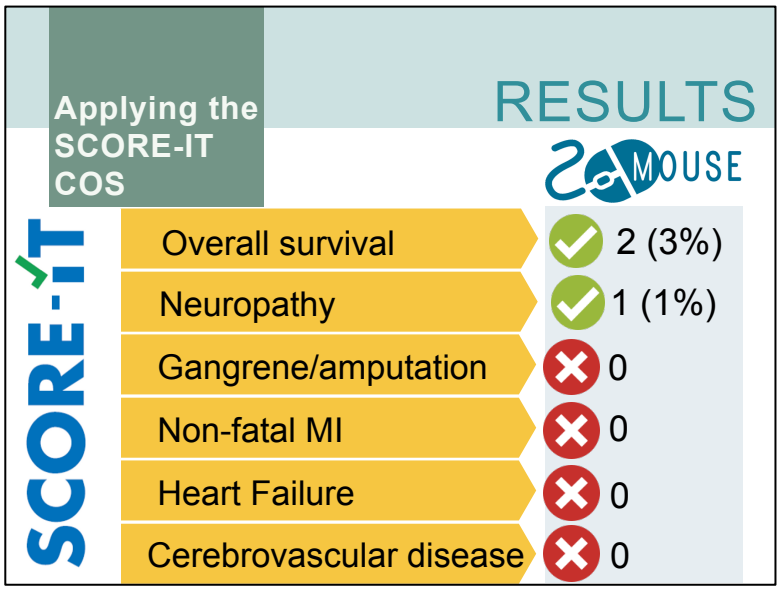
METHOD

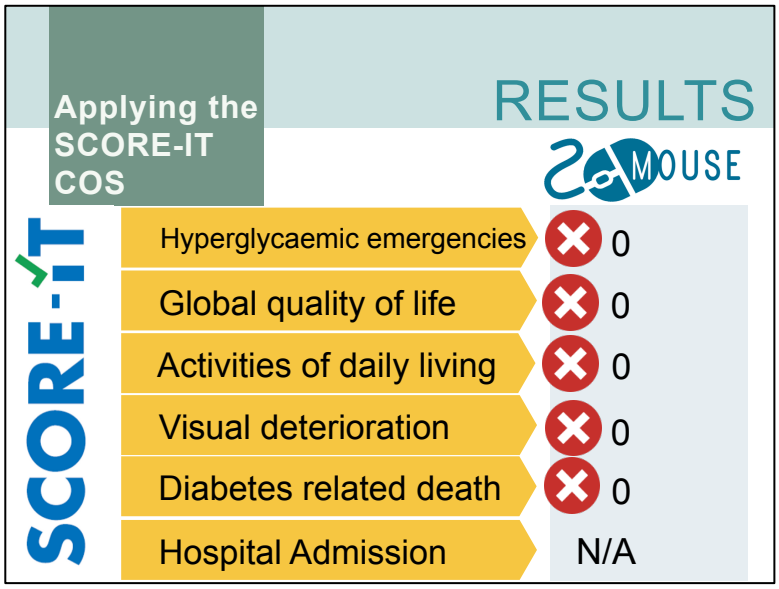
Pre-clinical studies of a pharmacological intervention aimed at lowering blood glucose in a mouse model of type 2 diabetes


Systematic Review
METHOD
9771 articles retrieved
1940 included at abstract screening
Sample of 72
486 reviewed
289 Included (3 ILLs pending)
25% sample in 10 year blocks selected for full text review


Outcomes Overview
RESULTS
81% of outcomes measured in pre-clinical studies were also measured in phase 3/4 trials.
COMOUSE
72 studies
544 individual outcomes
Median 5 outcomes per study (range 1-31)
Outcomes categorized into 11 domains*
SCORE-IT
138 studies
1444 individual outcomes
Median 8 outcomes per study (range 1-60)
Outcomes categorized into 30 domains*
* Dodd et al J Clin Epidemiol. 2018 Apr;96:84-92.


Applying the SCORE-IT COS
RESULTS
COMOUSE
SCORE-IT
Glycaemic control
73 (100%)
Hyperglycaemia
" considered to be measured if a study measured blood glucose
Hypoglycaemia
"
Body weight
41 (56%)
Side Effects
4 (5%)
Kidney function
2 (3%)





SUMMARY

Can a COS be applied to pre-clinical studies?

- 8/18 **(44%)** of COS outcomes have been measured in the sample of pre-clinical studies.
- Of the 18 outcomes in the SCORE-IT COS, 17 could theoretically be measured in mice.
- What are the barriers to applying the SCORE-IT COS to pre-clinical studies?

NEXT STEPS

Complete data extraction and outcome classification for the remaining papers.

Compare the COS with a parallel study looking at the “how” for pre-clinical animal studies.

Consider potential barriers to applying the SCORE-IT COS pre-clinically.

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